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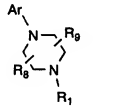
(54) Title: SUBSTITUTED ARYL PIPERAZINES AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

(57) **Abstract**

The present invention is directed to aryl piperazines of formula (I) (wherein Ar, R_1, R_8 and R_9 are defined herein) which are useful as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, and/or CXCR-4.



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TITLE OF THE INVENTION

SUBSTITUTED ARYL PIPERAZINES AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

BACKGROUND OF THE INVENTION

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation (reviewed in Schall, Cytokine, 3, 165-183 (1991) and Murphy, Rev. Immun., 12, 593-633 (1994)). There are two classes of chemokines, C-X-C (α) and C-C (β), depending on whether the first two cysteines are separated by a single amino acid (C-X-C) or are adjacent (C-C). The α-chemokines, such as interleukin-8 (IL-8), neutrophil-activating protein-2 (NAP-2) and melanoma growth stimulatory activity protein (MGSA) are chemotactic primarily for neutrophils, whereas β-chemokines, such as RANTES, MIP-1α, MIP-1β , monocyte chemotactic protein-1 (MCP-1), MCP-2, MCP-3 and eotaxin are chemotactic for macrophages, T-cells, eosinophils and basophils (Deng, et al., Nature, 381, 661-666 (1996)).

The chemokines bind specific cell-surface receptors belonging to the family of G-protein-coupled seven-transmembrane-domain proteins (reviewed in Horuk, Trends Pharm. Sci., 15, 159-165 (1994)) which are termed "chemokine receptors." On binding their cognate ligands, chemokine receptors transduce an intracellular signal though the associated trimeric G protein, resulting in a rapid increase in intracellular calcium concentration. There are at least seven human chemokine receptors that bind or respond to β-chemokines with the following characteristic pattern: CCR-1 (or "CKR-1" or "CC-CKR-1") [MIP-1α, MIP-1β, MCP-3, RANTES] (Ben-Barruch, et al., J. Biol. Chem., 270, 22123-22128 (1995); Beote, et al, Cell, 72, 415-425 (1993)); CCR-2A and CCR-2B (or "CKR-2A"/"CKR-2A" or "CC-CKR-2A"/"CC-CKR-2A") [MCP-1, MCP-3, MCP-4]; CCR-3 (or "CKR-3" or "CC-CKR-3") [eotaxin, RANTES, MCP-3] (Combadiere, et al., J. Biol. Chem., 270, 16491-16494 (1995); CCR-4 (or "CKR-4" or "CC-CKR-4") [MIP-1α, RANTES, MCP-1] (Power, et al., J. Biol. Chem., 270, 19495-19500 (1995)); CCR-5 (or "CKR-5" or "CC-CKR-5") [MIP-1α, RANTES, MIP-1β]

(Sanson, et al., Biochemistry, 35, 3362-3367 (1996)); and the Duffy blood-group antigen [RANTES, MCP-1] (Chaudhun, et al., J. Biol. Chem., 269, 7835-7838 (1994)). The β-chemokines include eotaxin, MIP ("macrophage inflammatory protein"), MCP ("monocyte chemoattractant protein") and RANTES ("regulation-upon-activation, normal T expressed and secreted").

Chemokine receptors, such as CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, CXCR-4, have been implicated as being important mediators of inflammatory and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. For example, the chemokine receptor CCR-3 plays a pivotal role in attracting eosinophils to sites of allergic inflammation. Accordingly, agents which modulate chemokine receptors would be useful in such disorders and diseases.

A retrovirus designated human immunodeficiency virus (HIV-1) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV.

Certain compounds have been demonstrated to inhibit the replication of HIV, including soluble CD4 protein and synthetic derivatives (Smith, et al., Science, 238, 1704-1707 (1987)), dextran sulfate, the dyes Direct Yellow 50, Evans Blue, and certain azo dyes (U.S. Patent No. 5,468,469). Some of these antiviral agents have been shown to act by blocking the binding of gp120, the coat protein of HIV, to its target, the CD4 gyycoprotein of the cell.

Entry of HIV-1 into a target cell requires cell-surface CD4 and additional host cell cofactors. Fusin has been identified as a cofactor required for infection with virus adapted for growth in transformed T-cells, however, fusin does not promote entry of macrophagetropic viruses which are believed to be the key pathogenic strains of HIV in vivo. It has recently been recognized that for efficient entry into target cells, human immunodeficiency viruses require the chemokine

receptors CCR-5 and CXCR-4, as well as the primary receptor CD4 (Levy, N. Engl. J. Med., 335(20), 1528-1530 (Nov. 14 1996). The principal cofactor for entry mediated by the envelope glycoproteins of primary macrophage-trophic strains of HIV-1 is CCR5, a receptor for the β-chemokines RANTES, MIP-1α and MIP-1β (Deng, et al., Nature, 381, 661-666 (1996)). HIV attaches to the CD4 molecule on cells through a region of its envelope protein, gp120. It is believed that the CD-4 binding site on the gp120 of HIV interacts with the CD4 molecule on the cell surface, and undergoes conformational changes which allow it to bind to another cell-surface receptor, such as CCR5 and/or CXCR-4. This brings the viral envelope closer to the cell surface and allows interaction between gp41 on the viral envelope and a fusion domain on the cell surface, fusion with the cell membrane, and entry of the viral core into the cell. Macrophage-tropic HIV and SIV envelope proteins have been shown to induce a signal through CCR-5 on CD4+ cells resulting in chemotaxis of T cells which may enhance the replication of the virus (Weissman, et al., Nature, 389, 981-985 (1997)). It has been shown that β-chemokine ligands prevent HIV-1 from fusing with the cell (Dragic, et al., Nature, 381, 667-673 (1996)). It has further been demonstrated that a complex of gp120 and soluble CD4 interacts specifically with CCR-5 and inhibits the binding of the natural CCR-5 ligands MIP-1α and MIP-1β (Wu, et al., Nature, 384, 179-183 (1996); Trkola, et al., Nature, 384, 184-187 (1996)).

Humans who are homozygous for mutant CCR-5 receptors which do not serve as co-receptors for HIV-1 in vitro apper to be unusually resistant to HIV-1 infection and are not immuno-compromised by the presence of this genetic variant (Nature, 382, 722-725 (1996)). Similarly, an alteration in the CCR-2 gene, CCR2-641, can prevent the onset of full-blown AIDS (Smith, et al., Science, 277, 959-965 (1997). Absence of CCR-5 appears to confer protection from HIV-1 infection (Nature, 382, 668-669 (1996)). An inherited mutation in the gene for CCR5, Delta 32, has been shown to abolish functional expression of the gene and individuals homozygous for the mutation are apparently not susceptible to HIV infection. Other chemokine receptors may be used by some strains of HIV-1 or may be favored by non-sexual routes of

transmission. Although most HIV-1 isolates studied to date utilize CCR-5 or fusin, some can use both as well as the related CCR-2B and CCR-3 as co-receptors (Nature Medicine, 2(11), 1240-1243 (1996)). Nevertheless, drugs targeting chemokine receptors may not be unduly compromised by the genetic diversity of HIV-1 (Zhang, et al., Nature, 383, 768 (1996)). The β-chemokine macrophage-derived chemokine (MDC) has been shown to inhibit HIV-1 infection (Pal, et al., Science, 278 (5338), 695-698 (1997). The chemokines RANTES, MIP-1α, MIP-1β, vMIP-I, vMIP-II, SDF-1 have also been shown to suppress HIV. A derivative of RANTES, (AOP)-RANTES, is a subnanomolar antagonist of CCR-5 function in monocytes (Simmons, et al., Science, 276, 276-279 (1997)). Monoclonal antibodies to CCR-5 have been reported to block infection of cells by HIV in vitro. Accordingly, an agent which could block chemokine receptors in humans who possess normal chemokine receptors should prevent infection in healthy individuals and slow or halt viral progression in infected patients (see Science, 275, 1261-1264 (1997)). By focusing on the host's cellular immune response to HIV infection, better therapies towards all subtypes of HIV may be provided. These results indicate that inhibition of chemokine receptors presents a viable method for the prevention or treatment of infection by HIV and the prevention or treatment of AIDS.

The peptides eotaxin, RANTES, MIP-1α, MIP-1β, MCP-1, and MCP-3 are known to bind to chemokine receptors. As noted above, the inhibitors of HIV-1 replication present in supernatants of CD8+ T cells have been characterized as the β-chemokines RANTES, MIP-1α and MIP-1β. PCT Patent Publications WO 94/17045 (published August 4, 1994), WO 94/29309 (published December 22, 1994), and WO 96/10568 (published April 11, 1996) disclose certain azacycles as tachykinin antagonists.

SUMMARY OF THE INVENTION

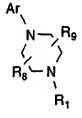
The present invention is directed to compounds which are modulators of chemokine receptor activity and are useful in the prevention or treatment of certain inflammatory and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well

as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which chemokine receptors are involved.

The present invention is further concerned with compounds which inhibit the entry of human immunodeficiency virus (HIV) into target cells and are of value in the prevention of infection by HIV, the treatment of infection by HIV and the prevention and/or treatment of the resulting acquired immune deficiency syndrome (AIDS). The present invention also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds and other agents for the prevention and treatment of AIDS and viral infection by HIV.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of Formula I:



I

wherein the nitrogen attached to R_1 shown above is optionally quaternized with C_{1-4}alkyl or phenylC_{1-4}alkyl or is optionally present as the N-oxide (N^+O^-), and wherein:

R_1 is selected from a group consisting of:

linear or branched C_{1-8} alkyl, linear or branched C_{2-8} alkenyl, wherein the C_{1-8} alkyl or C_{2-8} alkenyl is optionally

mono, di, tri or tetra substituted, the substituents independently selected from:

(a) hydroxy,
(b) oxo,
(c) cyano,
(d) halogen which is defined to include Br, Cl, I, and F,
(e) trifluoromethyl,
(f) phenyl or mono, di or tri-substituted phenyl, the substituents independently selected from
  (1') phenyl,
  (2') hydroxy,
  (3') C_{1-3}alkyl,
  (4') cyano,
  (5') halogen,
  (6') trifluoromethyl,
  (7') $-NR_6COR_7$,
  (8') $-NR_6CO_2R_7$,
  (9') $-NR_6CONHR_7$,
  (10') $-NR_6S(O)jR_7$, wherein j is 1 or 2,
  (11') $-CONR_6R_7$,
  (12') $-COR_6$,
  (13') $-CO_2R_6$,
  (14') $-OR_6$,
  (15') $-S(O)_kR_6$, wherein k is 0, 1 or 2,
(g) $-NR_6R_7$,
(h) $-NR_6COR_7$,
(i) $-NR_6CO_2R_7$,
(j) $-NR_6CONHR_7$,
(k) $-NR_6S(O)j-R_7$,
(l) $-CONR_6R_7$,
(m) $-COR_6$,
(n) $-CO_2R_6$,
(o) $-OR_6$,
(p) $-S(O)_kR_6$,
(q) $-NR_6CO$-heteroaryl,

(r) -$NR_6S(O)_j$-heteroaryl, and

(s) heteroaryl, wherein heteroaryl is selected from the group consisting of:

(1') benzimidazolyl,
(2') benzofuranyl,
(3') benzoxazolyl,
(4') furanyl,
(5') imidazolyl,
(6') indolyl,
(7') isooxazolyl,
(8') isothiazolyl,
(9') oxadiazolyl,
(10') oxazolyl,
(11') pyrazinyl,
(12') pyrazolyl,
(13') pyridyl,
(14') pyrimidyl,
(15') pyrrolyl,
(16') quinolyl,
(17') tetrazolyl,
(18') thiadiazolyl,
(19') thiazolyl,
(20') thienyl, and
(21') triazolyl,

wherein the heteroaryl is unsubstituted or mono di or tri-substituted, the substituents independently selected from:

(a") phenyl,
(b") hydroxy,
(c") oxo,
(d") cyano,
(e") halogen, and
(f") trifluoromethyl;

Ar is selected from the group consisting of:

(1) phenyl,
(2) pyridyl,
(3) pyrimidyl,
(4) naphthyl,
(5) furyl,
(6) pyrryl,
(7) thienyl,
(8) isothiazolyl,
(9) imidazolyl,
(10) benzimidazolyl,
(11) tetrazolyl,
(12) pyrazinyl,
(13) quinolyl,
(14) isoquinolyl,
(15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,
(20) isoindolyl,
(21) purinyl,
(22) isoxazolyl,
(23) thiazolyl,
(24) oxazolyl,
(25) triazinyl, and
(26) benzthiazolyl,
(27) benzoxazolyl,
(28) imidazopyrazinyl,
(29) triazolopyrazinyl,
(30) naphthyridinyl,
(31) furopyridinyl,
(32) thiopyranopyrimidyl and the 5-oxide and 5-dioxide thereof,
(33) pyridazinyl,
(34) quinazolinyl,

(35) pteridinyl,
(36) triazolopyrimidyl,
(37) triazolopyrazinyl,
(38) thiapurinyl,
(39) oxapurinyl, and
(40) deazapurinyl,

wherein Ar items (1) to (40) are optionally mono or di-substituted, said substituents being independently selected from:

(a) C_{1-3} alkyl, unsubstituted or substituted with
  (1') oxo,
  (2') hydroxy,
  (3') OR_6,
  (4') halogen,
  (5') trifluoromethyl,
  (6') phenyl or mono, di or tri-substituted phenyl, the substituents independently selected from hydroxy, cyano, halogen, and trifluoromethyl,
(b) $-(CH_2)_nS(O)_k-(C_{1-6}$ alkyl), wherein n is 0, 1 or 2,
(c) $-(CH_2)_nS(O)j-NH_2$,
(d) $-(CH_2)_nS(O)j-NH(C_{1-6}$ alkyl),
(e) $-(CH_2)_nS(O)j-NHR_6$,
(f) $-(CH_2)_nS(O)j-NR_6-(C_{1-6}$ alkyl),
(g) $-(CH_2)_nCONH_2$,
(h) $-(CH_2)_nCONH-(C_{1-6}$ alkyl),
(i) $-(CH_2)_nCONHR_6$,
(j) $-(CH_2)_nCONR_6-(C_{1-6}$ alkyl),
(k) $-(CH_2)_nCO_2H$,
(l) $-(CH_2)_nCO_2-(C_{1-6}$ alkyl),
(m) $-(CH_2)_nNR_6R_7$,
(n) $-(CH_2)_nNH-C(O)-C_{1-6}$alkyl,
(o) $-(CH_2)_nNH-C(O)NH_2$,
(p) $-(CH_2)_nNH-C(O)NHC_{1-6}$alkyl,
(q) $-(CH_2)_nNH-C(O)N-(diC_{1-6}$ alkyl),
(r) $-(CH_2)_nNH-S(O)k-C_{1-6}$alkyl,
(s) $-(CH_2)_nN(C_{1-3}$alkyl)$-C(O)-N(diC_{1-6}$ alkyl),

(t) -$(CH_2)_n$-heteroaryl, -C(O)-heteroaryl or -$(CH_2)_n$-O-heteroaryl , wherein the heteroaryl is selected from the group consisting of:

(1') benzimidazolyl,
(2') benzofuranyl,
(3') benzoxazolyl,
(4') furanyl,
(5') imidazolyl,
(6') indolyl,
(7') isooxazolyl,
(8') isothiazolyl,
(9') oxadiazolyl,
(10') oxazolyl,
(11') pyrazinyl,
(12') pyrazolyl,
(13') pyridyl or oxopyridyl,
(14') pyrimidyl,
(15') pyrrolyl,
(16') quinolyl,
(17') tetrazolyl,
(18') thiadiazolyl,
(19') thiazolyl,
(20') thienyl, and
(21') triazolyl,

wherein the heteroaryl group of items (1') to (21') is unsubstituted, mono, di or tri substituted, the substituents selected from:

(a') hydrogen,
(b') C_{1-6} alkyl, branched or unbranched, unsubstituted or mono or di-substituted, the substituents being selected from hydrogen and hydroxy,
(c') hydroxy,
(d') oxo,

(e') -OR_6,
(f') halogen,
(g') trifluoromethyl,
(h') nitro,
(i') cyano,
(j') -NHR_6,
(k') -NR_6R_7,
(l') -$NHCOR_6$,
(m') -NR_6COR_7,
(n') -$NHCO_2R_6$,
(o') -$NR_6CO_2R_7$,
(p') -$NHS(O)_jR_6$,
(q') -$NR_6S(O)_jR_7$,
(r') -$CONR_6R_7$,
(s') -COR_6,
(t') -CO_2R_6, and
(u') -$S(O)_jR_6$;

R_6 is selected from:

(1) hydrogen,
(2) C_{1-6} alkyl, or mono or di-substituted C_{1-6} alkyl, the substituents independently selected from:
  (a) phenyl,
  (b) hydroxy,
  (c) oxo,
  (d) cyano,
  (e) halogen,
  (f) trifluoromethyl, and
(3) phenyl or mono di or tri-substituted phenyl, the substituents independently selected from:
  (a) hydroxy,
  (b) C_{1-3}alkyl,
  (c) cyano,
  (d) halogen,

(e) trifluoromethyl;

R_7 is selected from:

(1) hydrogen,

(2) C_{1-6} alkyl, or mono or di-substituted C_{1-6} alkyl, the substituents independently selected from:

(a) phenyl unsubstituted or substituted with

(1') hydroxy,

(2') C_{1-3}alkyl,

(3') cyano,

(4') halogen,

(5') trifluoromethyl,

(6') C_{1-3}alkyloxy,

(b) hydroxy,

(c) oxo,

(d) cyano,

(e) halogen,

(f) trifluoromethyl,

(3) phenyl or mono di or tri-substituted phenyl, the substituents independently selected from:

(a) hydroxy,

(b) C_{1-3}alkyl,

(c) cyano,

(d) halogen,

(e) trifluoromethyl,

(4) naphthyl or mono di or tri-substituted naphthyl, the substituents independently selected from:

(a) hydroxy,

(b) C_{1-3}alkyl,

(c) cyano,

(d) halogen,

(e) trifluoromethyl,

(5) C_{1-3}alkyloxy;

or R_6 and R_7 are joined together to form a 5-, 6-, or 7-

membered monocyclic saturated ring containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and in which the ring is unsubstituted or mono or di-substituted, the substituents independently selected from:

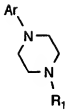
(1) hydroxy,
(2) oxo,
(3) cyano,
(4) halogen,
(5) trifluoromethyl,

R_8 and R_9 are each independently hydrogen or substituted C_{1-4}alkyl wherein the substitutent is selected from the group consisting of

(1) hydroxy,
(2) hydrogen,
(3) cyano,
(4) halogen,
(5) trifluoromethyl,
(6) C_{1-3}alkyloxy,

provided that when Ar is phenyl, pyridyl or pyrimidyl, then Ar is mono di or tri-substituted;
and further provided that when Ar is mono substituted phenyl, then the substituent is other than halo, hydroxy, -OC_{1-4}alkyl, CF_3 or C_{1-4}alkyl;
and further provided that when Ar is di- or tri-substituted, at least one of the substituents is other than halo, hydroxy, -OC_{1-4}alkyl, CF_3 or C_{1-4}alkyl;
and pharmaceutically acceptable salts thereof.

Preferred compounds for use in the present invention include those of Formula Ia:



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wherein:

R_1 is selected from a group consisting of:

C_3, C_4, C_5, C_6, C_7, C_8 linear or branched alkyl, unsubstituted or mono, di or tri-substituted, the substituents independently selected from:

(a) hydroxy,

(b) Cl or F,

(c) phenyl or mono, di or tri-substituted phenyl, the substituents independently selected from:

(1') phenyl,

(2') hydroxy,

(3') C_{1-3}alkyl,

(4') cyano,

(5') halogen,

(6') trifluoromethyl,

(d) -NR_6CO-R7, wherein R_6 is hydrogen or C_{1-3} alkyl and R7 is phenyl optionally substituted with Cl, F, CF_3 or C_{1-3}alkyl,

(e) -COR_6,

(f) -OR_6,

(g) -$NR_6S(O)_j$-R7, where j is 1 or 2,

(h) -$NR_6S(O)_j$-heteroaryl, wherein heteroaryl is selected from the group consisting of:

(1') benzimidazolyl,

(2') benzofuranyl,

(3') benzoxazolyl,

(4') furanyl,
(5') imidazolyl,
(6') indolyl,
(7') isooxazolyl,
(8') isothiazolyl,
(9') oxadiazolyl,
(10') oxazolyl,
(11') pyrazinyl,
(12') pyrazolyl,
(13') pyridyl,
(14') pyrimidyl,
(15') pyrrolyl,
(16') quinolyl,
(17') tetrazolyl,
(18') thiadiazolyl,
(19') thiazolyl,
(20') thienyl, and
(21') triazolyl,

wherein the heteroaryl is unsubstituted or mono di or tri-substituted, the substituents independently selected from:

(a') phenyl,
(b') hydroxy,
(c') oxo,
(d') cyano,
(e') halogen, and
(f') trifluoromethyl;

Ar is selected from the group consisting of:

(1) phenyl,
(2) pyrazinyl,
(3) pyrazolyl,
(4) pyridyl,
(5) pyrimidyl, and
(6) thienyl,

wherein the Ar is unsubstituted or mono or di-substituted, and substituents are independently selected from:

(a) C_{1-3} alkyl, unsubstituted or substituted with
  (1') oxo,
  (2') hydroxy,
  (3') OR_6,
  (4') halogen, and
  (5') trifluoromethyl,
(b) $CONR_6$-(C_{1-2} alkyl),
(c) CO_2H,
(d) CO_2-(C_{1-2} alkyl),
(e) CH_2NR_6-(C_{1-2} alkyl),
(f) CH_2NH-C(O)-C_{1-3}alkyl,
(h) CH_2NH-C(O)NH_2,
(i) CH_2NH-C(O)NHC_{1-3}alkyl,
(j) CH_2NH-C(O)N-diC_{1-3} alkyl),
(k) CH_2NH-S(O)j-C_{1-3}alkyl,
(l) CH_2-heteroaryl, with the heteroaryl is selected from the group consisting of:
  (1') imidazolyl,
  (2') oxazolyl,
  (3') pyridyl,
  (4') tetrazolyl,
  (5') triazolyl,

and the heteroaryl is unsubstituted, mono, di or tri-substituted, where the substituents selected from:
  (a') hydrogen,
  (b') C_{1-6} alkyl, branched or unbranched, unsubstituted or mono or di-substituted, the substituents being selected from hydrogen and hydroxy;

and pharmaceutically acceptable salts thereof.

Preferred compounds for use in the present invention include those of Formula I wherein:

R_1 is selected from a group consisting of:

C_4, C_5, C_6, C_7 or C_8 linear or branched alkyl, which is mono, di- or tri-substituted, where the substituents are independently selected from:

(a) hydroxy,

(b) Cl or F,

(c) phenyl or mono or di-substituted phenyl, where the substituents are independently selected from:

(1') hydroxy,

(2') methyl or ethyl,

(3') Cl or F,

(4') trifluoromethyl,

(d) $-NR_6COR_7$, wherein R_6 is methyl and R_7 is phenyl optionally substituted with halo, CF_3, C_{1-3}alkyl or C_{1-3}alkoxy, and

(e) $-NR_6S(O)j-R_7$, where j is 1 or 2;

and pharmaceutically acceptable salts thereof.

Preferred compounds for use in the present invention include those of Formula I wherein:

Ar is mono substituted or di-substituted phenyl,

wherein the substituents are selected from the group consisting of:

(a) C_{1-3} alkyl, unsubstituted or substituted with

(1') oxo,

(2') hydroxy, or

(3') OR_6, wherein R_6 is hydrogen or C_{1-3} alkyl,

(b) $-CH_2NR_6-(C_{1-2}$ alkyl),

(c) $-CH_2NH-C(O)-C_{1-3}$alkyl,

(d) $-CH_2NH-C(O)NH_2$,

(i) $-CH_2NH-C(O)NHC_{1-3}$alkyl,

(j) $-CH_2NH-C(O)N-diC_{1-3}$ alkyl),

(k) $-CH_2NH-S(O)j-C_{1-3}$alkyl,

(l) $-CH_2$-heteroaryl, where heteroaryl is selected from the group consisting of:

(1') imidazolyl,

(2') oxazolyl,

(3') pyridyl,

(4') tetrazolyl,

(5') triazolyl,

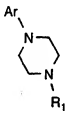
and where heteroaryl is unsubstituted, mono, di or tri substituted, where the substituents are independently selected from:

(a') hydrogen,

(b') C_{1-6} alkyl, branched or unbranched, unsubstituted or mono or disubstituted, where the substituents are selected from: hydrogen and hydroxy;

and pharmaceutically acceptable salts thereof.

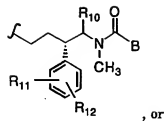
Preferred compounds for use in the present invention include those of Formula Ia:



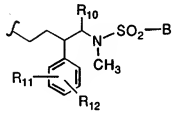
Ia

wherein:

R_1 is



, or



;

where B is selected from:

(a) phenyl, naphthyl, mono, di or tri-substituted phenyl, and mono, di or tri-substituted naphthyl wherein the substituents on phenyl or naphthyl are independently selected from: chloro, methyl, phenyl, C_{1-3}alkoxy, and CF_3;

(b) -CH_2phenyl, and mono or di-substituted -CH_2phenyl wherein the substituents on phenyl are independently selected from: chloro, methyl, phenyl, C_{1-3}alkoxy and CF_3;

(c) pyridyl, and mono di or tri-substituted pyridyl wherein the substituents on pyridyl are independently selected from: chloro, methyl, phenyl, C_{1-3}alkoxy and CF_3; and

(d) thiophene, and mono or disubstituted thiophene wherein the substituents on thiophene are independently selected from: chloro, methyl, phenyl, C_{1-3}alkoxy and CF_3;

Ar is mono substituted phenyl wherein the substituent is selected from the group consisting of:

(a) -CH_2-tetrazolyl,

(b) -CH_2-triazolyl,

(c) -CH_2-imidazolyl,

(d) -CH_2-N(H)C(O)N$(CH_3)_2$,

(e) $-CH_2-N(H)C(O)N(H)CH_3$,
(f) $-CH_2-N(H)C(O)CH_3$,
(g) $-CH_2-N(H)S(O)_2CH_3$,
(h) $-CH_2$-pyridyl,
(i) $-CH_2$-oxopyridyl,
(j) $-CH_2$-O-pyridyl, and
(k) mono or di-substituted purine wherein the substituents are selected from:
(1') C_{1-3}alkyl,
(2') C_{1-3}alkoxy,
(3') fluoro,
(4') hydrogen, and
(5') fluoroC_{1-3}alkyl;

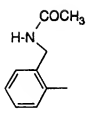
R_{10} is selected from: hydrogen, C_{1-3}alkyl, and phenyl;

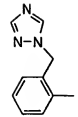
R_{11} and R_{12} are independently selected from:
hydrogen, halogen, methyl, phenyl or CF_3;

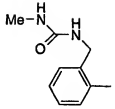
and pharmaceutically acceptable salts thereof.

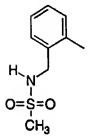
Even more preferred compounds for use in the present invention include those of Formula Ia wherein B is unsubstituted phenyl or unsubstituted thiophene.

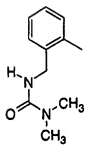
Illustrating the present invention is the use of the compounds wherein Ar is selected from

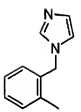


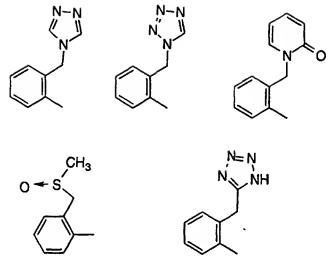




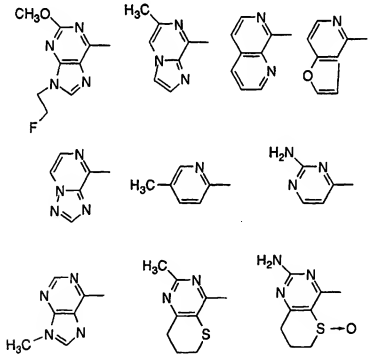




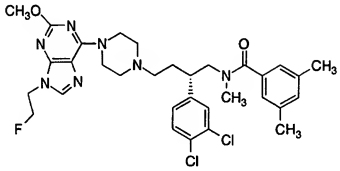


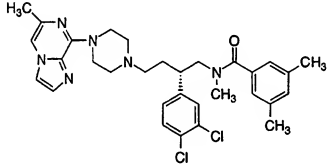


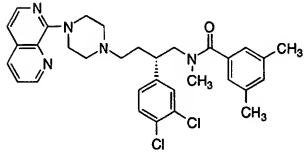
Another embodiment of compounds which are useful in the present invention is directed to compounds of Formula I wherein Ar is selected from the group consisting of:

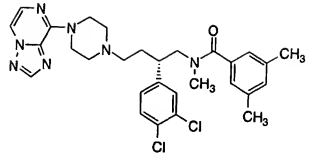


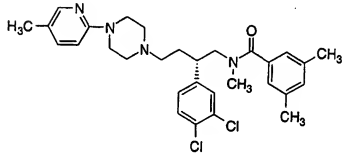
Exemplifying the present invention is the use of a compound selected from the group consisting of:

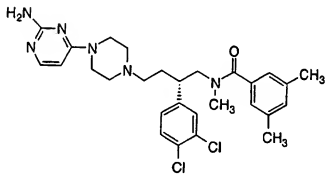












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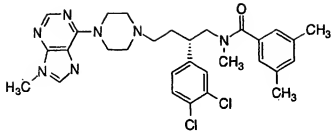

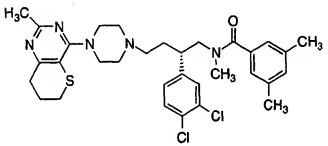

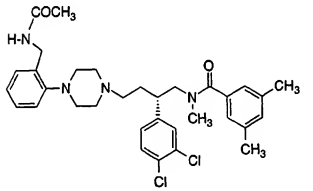

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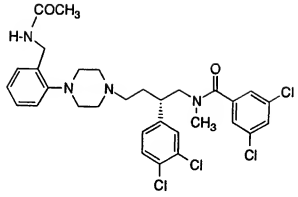
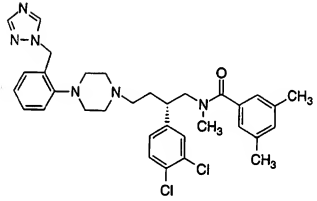
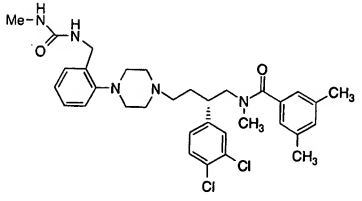
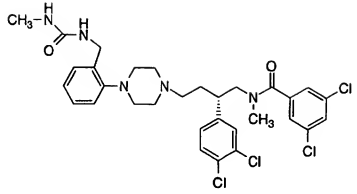
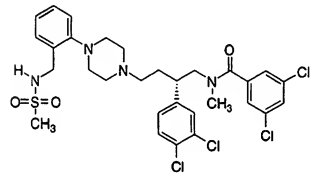
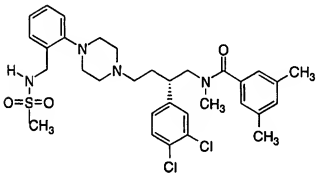


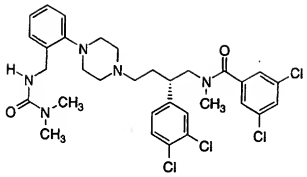


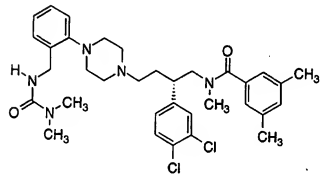


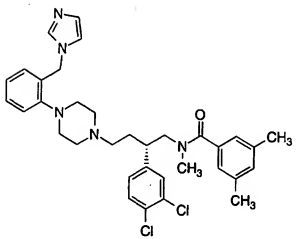


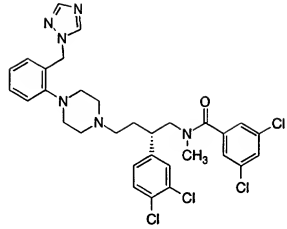


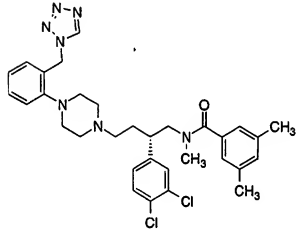


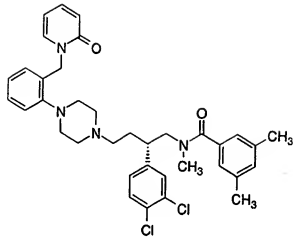


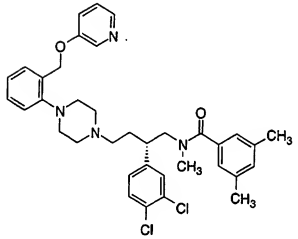


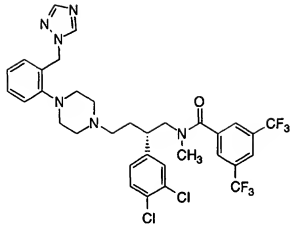


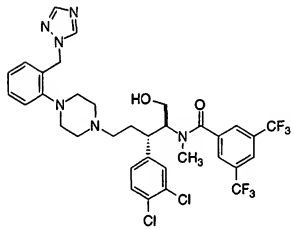








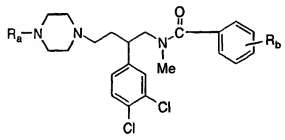




As appreciated by those of skill in the art, halo as used herein are intended to include chloro, fluoro, bromo and iodo. Similarly, C1-6, as in C_{1-6}alkyl is defined to identify the group as having 1, 2, 3, 4, 5, or 6 carbons, such that C_{1-6}alkyl specifically includes methyl, ethyl, propyl, butyl, pentyl or hexyl

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein.

Specific compounds of use in the present invention include compounds of the formula:



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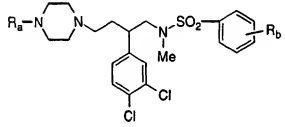
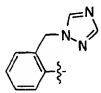
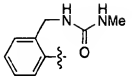


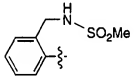
wherein:

R_a	R_b
	3,5-diMe
	3,5-diCl
	3,5-diCF3
	3,5-diMe
	3,5-diCl
	3,5-diCF3


3,5-diMe

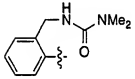
3,5-diCl

3,5-diCF3


3,5-diMe

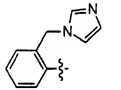
3,5-diCl

3,5-diCF3

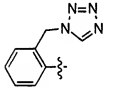

3,5-diMe

3,5-diCl

3,5-diCF3


3,5-diMe

3,5-diCF3


3,5-diMe

3,5-diCF3

and pharmaceutically acceptable salts thereof.

Specific compounds of use in the present invention include:

(a) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-((2-acetylaminomethyl)-phenyl)-piperazine;

(b) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl-(methylamino))butyl)-4-(2-acetylaminomethylphenyl)-piperazine;

(c) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethyl-benzoyl-(methylamino))butyl)-4-((2-methylaminocarbonylamino-methyl) phenyl)-piperazine;

(d) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethyl-benzoyl (methylamino))butyl)-4-((2-dimethylaminocarbonylamino-methyl) phenyl)-piperazine;

(e) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethyl-benzoyl-(methylamino))butyl)-4-(2-methylsulfonylaminomethyl-phenyl)-piperazine;

(f) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichloro-benzoyl-(methylamino))butyl)-4-((2-methylaminocarbonylamino-methyl) phenyl)-piperazine;

(g) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichloro-benzoyl-(methylamino))butyl)-4-((2-dimethylaminocarbonylamino-methyl) phenyl)-piperazine;

(h) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichloro-benzoyl-(methylamino))butyl)-4-(2-methylsulfonylaminomethyl-phenyl)-piperazine;

(i) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethyl-benzoyl-(methylamino))butyl)-4-(2-((1'-imidazolyl)methyl)phenyl)-piperazine;

(j) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichloro-benzoyl-(methylamino))butyl)-4-(2-(1'-(1',2',4'-triazolyl)methyl-phenyl)-piperazine;

(k) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethyl-benzoyl-(methylamino))butyl)-4-(2-(1'-(1',2',4'-triazolyl)methyl-phenyl)-piperazine;

(l) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethyl-benzoyl-(methylamino))butyl)-4-(2-(1'-(1',2',3',4'-tetrazolyl)methyl-phenyl)-piperazine;

(m) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethyl-benzoyl-(methylamino))butyl)-4-(2-(3'-pyridyloxy)methylphenyl)-piperazine;

(n) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethyl-benzoyl-(methylamino))butyl)-4-(2-(1'-(2'(1'H)-pyridone)methyl-phenyl)-piperazine;

(o) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(2-amino-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine-5-oxide;

(p) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(2-methyl-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine-5-oxide;

(q) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethyl-benzoyl)-(methylamino))butyl)-4-(9-(2-fluoroethyl)-2-methoxy-purin-6-yl) piperazine;

(r) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethyl-benzoyl)-(methylamino))butyl)-4-(9-(2-methoxymethyl)-2-methoxy-purin-6-yl) piperazine;

(s) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethyl-benzoyl)-(methylamino))butyl)-4-(9-methyl-purin-6-yl)piperazine;

(t) 1-(3-((S)-(4-Dichlorophenyl))-4-(N-(3,5-dimethyl-benzoyl)-(methylamino))butyl)-4-(9-methyl-purin-6-yl)piperazine;

(u) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethyl-benzoyl)-(methylamino))butyl)-4-(6-methyl-imidazo(1,2-a)pyrazin-1-yl) piperazine;

(v) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethyl-benzoyl)-(methylamino))butyl)-4-(1,7-naphthyridin-8-yl)piperazine;

(w) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethyl-benzoyl)-(methylamino))butyl)-4-(1,2,4-triazolo(1,5-a)pyrazin-8-yl)piperazine;

(x) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethyl-benzoyl)-(methylamino))butyl)-4-(5-methyl-pyrid-2-yl)piperazine;

(y) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethyl-benzoyl)-(methylamino))butyl)-4-(2-amino-pyrazin-4-yl)piperazine;

(z) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethyl-benzoyl)-(methylamino))butyl)-4-(furo(2,3-c)pyrid-4-yl))piperazine;

(aa) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-amino-7,8-dihydro-6H-thiopyrano-(3,2-d)pyrimid-4-yl)piperazine;

(ab) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-methyl-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine;

(ac) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-bis(trifluoromethyl)benzoyl)-(methylamino))butyl)-4-(1,2,4-triazolo(1,5-a)pyrazin-8-yl)piperazine; and

(ad) 1-(3-((S)-(4-Chlorophenyl))-4-(N-(3,5-bis(trifluoromethyl)benzoyl)-(methylamino))butyl)-4-(1,2,4-triazolo(1,5-a)pyrazin-8-yl)piperazine;

and pharmaceutically acceptable salts thereof.

The subject compounds are useful in a method of modulating chemokine receptor activity in a patient in need of such modulation comprising the administration of an effective amount of the compound.

The present invention is directed to the use of the foregoing spiro-substituted azacycles as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors, including CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, and/or CXCR-4.

With respect to activity as modulators of the chemokine receptor CCR-5 it is preferred that in the subject compounds R_1 is alkyl which bears a substituent -$NR_6S(O)_j$-R_7, where R_6, R_7 and j are defined above.

The present invention is further directed to the use of compounds of this general structure which are disclosed as being antagonists of neurokinin receptors. Such compounds are disclosed, for example, in: U.S. Patent No. 5,317,020; U.S. Patent No. 5,534,525; U.S. Patent No. 5,350,852; U.S. Patent No. 5,411,971; U.S. Patent No. 5,446,052; U.S. Patent No. 5,560,700; EP 0 559 538, Sep. 8, 1993; EP 0 591 040, Apr. 6, 1994; EP 0 698 601, Feb. 28, 1996; EP 0 625 509, Nov. 23, 1994; EP 0 630 887, Dec. 28, 1994; EP 0 680 962, Nov. 8, 1995; EP 0 709 375, May 1, 1996; EP 0 709 376, May 1, 1996; EP 0 723 959, Jul. 31, 1996; EP 0 739 891; WO

94/10146, May 11, 1994; WO 94/17045, Aug. 4, 1994; WO 94/26735, Nov. 24, 1994; WO 94/29309, Dec. 22, 1994; WO 95/05377, Feb. 23, 1995; WO 95/12577, May 11, 1995; WO 95/15961, Jun. 15, 1995; WO 95/16682, Jun. 22, 1995; WO 95/21187; WO 95/26335, Oct. 5, 1995; WO 95/26338, Oct. 5, 1995; WO 95/35279; WO 96/06094, Feb. 29, 1996; WO 96/10568, Apr. 11, 1996; WO 96/23787, Aug. 8, 1996; WO 96/24582, Aug. 15, 1996; WO 96/28441; and WO 96/32385. Accordingly, the present invention embraces the use of a compound disclosed in these publications as a modulator of chemokine receptor activity.

The utility of the compounds in accordance with the present invention as modulators of chemokine receptor activity may be demonstrated by methodology known in the art, such as the assay for CCR-1 and/or CCR-5 binding as disclosed by Van Riper, et al., J. Exp. Med., 177, 851-856 (1993), and the assay for CCR-2 and/or CCR-3 binding as disclosed by Daugherty, et al., J. Exp. Med., 183, 2349-2354 (1996). Cell lines for expressing the receptor of interest include those naturally expressing the receptor, such as EOL-3 or THP-1, or a cell engineered to express a recombinant receptor, such as CHO, RBL-2H3, HEK-293. For example, a CCR3 transfected AML14.3D10 cell line has been placed on restricted deposit with American Type Culture Collection in Rockville, Maryland as ATCC No. CRL-12079, on April 5, 1996. The utility of the compounds in accordance with the present invention as inhibitors of the spread of HIV infection in cells may be demonstrated by methodology known in the art, such as the HIV quantitation assay disclosed by Nunberg, et al., J. Virology, 65 (9), 4887-4892 (1991).

In particular, the compounds of the following examples had activity in binding to either the CCR-5 receptor or the CCR-3 receptor in the aforementioned assays. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity.

Mammalian chemokine receptors provide a target for interfering with or promoting eosinophil and/or lymphocyte function in a mammal, such as a human. Compounds which inhibit or promote chemokine receptor function, are particularly useful for modulating eosinophil and/or lymphocyte function for therapeutic purposes.

Accordingly, the present invention is directed to compounds which are useful in the prevention and/or treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis.

For example, an instant compound which inhibits one or more functions of a mammalian chemokine receptor (e.g., a human chemokine receptor) may be administered to inhibit (i.e., reduce or prevent) inflammation. As a result, one or more inflammatory processes, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, is inhibited. For example, eosinophilic infiltration to inflammatory sites (e.g., in asthma) can be inhibited according to the present method.

Similarly, an instant compound which promotes one or more functions of a mammalian chemokine receptor (e.g., a human chemokine) is administered to stimulate (induce or enhance) an inflammatory response, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, resulting in the beneficial stimulation of inflammatory processes. For example, eosinophils can be recruited to combat parasitic infections.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

Diseases and conditions associated with inflammation and infection can be treated using the method of the present invention. In a preferred embodiment, the disease or condition is one in which the actions of eosinophils and/or lymphocytes are to be inhibited or promoted, in order to modulate the inflammatory response.

Diseases or conditions of humans or other species which can be treated with inhibitors of chemokine receptor function, include,

but are not limited to: inflammatory or allergic diseases and conditions, including respiratory allergic diseases such as asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), delayed-type hypersentitivity, interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes; glomerulonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including allograft rejection or graft-versus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis); eosinphilic myositis, eosinophilic fasciitis; cancers with leukocyte infiltration of the skin or organs. Other diseases or conditions in which undesirable inflammatory responses are to be inhibited can be treated, including, but not limited to, reperfusion injury, atherosclerosis, certain hematologic malignancies, cytokine-induced toxicity (e.g., septic shock, endotoxic shock), polymyositis, dermatomyositis.

Diseases or conditions of humans or other species which can be treated with promoters of chemokine receptor function, include, but are not limited to: immunosuppression, such as that in individuals with immunodeficiency syndromes such as AIDS, individuals undergoing radiation therapy, chemotherapy, therapy for autoimmune disease or other drug therapy (e.g., corticosteroid therapy), which causes immunosuppression; immunosuppression due congenital deficiency in receptor function or other causes; and infectious diseases, such as parasitic diseases, including, but not limited to helminth

infections, such as nematodes (round worms); (Trichuriasis, Enterobiasis, Ascariasis, Hookworm, Strongyloidiasis, Trichinosis, filariasis); trematodes (flukes) (Schistosomiasis, Clonorchiasis), cestodes (tape worms) (Echinococcosis, Taeniasis saginata, Cysticercosis); visceral worms, visceral larva migrans (e.g., Toxocara), eosinophilic gastroenteritis (e.g., Anisaki spp., *Phocanema ssp.),* cutaneous larva migrans (*Ancylostona braziliense, Ancylostoma caninum*).

The compounds of the present invention are accordingly useful in the prevention and treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases.

In another aspect, the instant invention may be used to evaluate putative specific agonists or antagonists of chemokine receptors, including CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, and CXCR-4. Accordingly, the present invention is directed to the use of these compounds in the preparation and execution of screening assays for compounds which modulate the activity of chemokine receptors. For example, the compounds of this invention are useful for isolating receptor mutants, which are excellent screening tools for more potent compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other compounds to chemokine receptors, e.g., by competitive inhibition. The compounds of the instant invention are also useful for the evaluation of putative specific modulators of the chemokine receptors, including CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, and CXCR-4. As appreciated in the art, thorough evaluation of specific agonists and antagonists of the above chemokine receptors has been hampered by the lack of availability of non-peptidyl (metabolically resistant) compounds with high binding affinity for these receptors. Thus the compounds of this invention are commercial products to be sold for these purposes.

The present invention is further directed to a method for the manufacture of a medicament for modulating chemokine receptor activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The present invention is further directed to the use of these compounds in the prevention or treatment of infection by a retrovirus, in particular, the human immunodeficiency virus (HIV) and the treatment of, and delaying of the onset of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, organ transplant, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery. In addition, a compound of the present invention may be used for the prevention of infection by HIV and the prevention of AIDS, such as in post-coital prophylaxis or in the prevention of maternal transmission of the HIV virus to a fetus or a child upon birth.

In a preferred aspect of the present invention, a subject compound may be used in a method of inhibiting the binding of a human immunodeficiency virus to a chemokine receptor, such as CCR-5 and/or CXCR-4, of a target cell, which comprises contacting the target cell with an amount of the compound which is effective at inhibiting the binding of the virus to the chemokine receptor.

The subject treated in the methods above is a mammal, preferably a human being, male or female, in whom modulation of chemokine receptor activity is desired. "Modulation" as used herein is intended to encompass antagonism, agonism, partial antagonism and/or partial agonism. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified

amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

Combined therapy to modulate chemokine receptor activity and thereby prevent and treat inflammatory and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis, and those pathologies noted above is illustrated by the combination of the compounds of this invention and other compounds which are known for such utilities.

For example, in the treatment or prevention of inflammation, the present compounds may be used in conjunction with an antiinflammatory or analgesic agent such as an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent, for example with a compound such as acetaminophen, asprin, codiene, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap, and the like. Similarly, the instant compounds may be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antiitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a sedating or non-sedating antihistamine. Likewise, compounds of the present invention may be used in combination with other drugs that are

used in the treatment/prevention/ suppression or amelioration of the diseases or conditions for which compounds of the pressent invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention. Examples of other active ingredients that may be combined with a compound of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) VLA-4 antagonists such as those described in US 5,510,332, WO97/03094, WO97/02289, WO96/40781, WO96/22966, WO96/20216, WO96/01644, WO96/06108, WO95/15973 and WO96/31206; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, rapamycin and other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as β2-agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen,

indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxican), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) other antagonists of the chemokine receptors, especially CCR-1, CCR-2, CCR-3 and CCR-5; (j) cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and colestipol), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; (k) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), α-glucosidase inhibitors (acarbose) and glitazones (troglitazone and pioglitazone); (l) preparations of interferon beta (interferon beta-1α, interferon beta-1β); (m) other compounds such as 5-aminosalicylic acid and prodrugs thereof, antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer chemotherapeutic agents. The weight ratio of the compound of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

The present invention is further directed to combinations of the present compounds with one or more agents useful in the prevention or treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, anti-infectives, or vaccines known to those of ordinary skill in the art.

ANTIVIRALS

Drug Name	Manufacturer	Indication
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase (RT) inhibitor)
141 W94	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
1592U89	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
Abacavir (1592U89)	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC

AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil	Gilead Sciences	HIV infection
AL-721	Ethigen (Los Angeles, CA)	ARC, PGL HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which neutralizes pH labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-232623 (CGP-73547)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
(-) 6-Chloro-4(S)-cyclopropylethynyl-4(S)-trifluoro-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one	Merck	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection

Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus immune globin	MedImmune	CMV retinitis
Cytovene Ganciclovir	Syntex	sight threatening CMV peripheral CMV retinitis
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-266	DuPont-Merck Pharmaceuticals	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
Efavirenz (DMP 266)	DuPont Merck	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)

EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Famciclovir	Smith Kline	herpes zoster, herpes simplex
FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GW 141	Glaxo Welcome	HIV infection, AIDS, ARC (protease inhibitor)
GW 1592	Glaxo Welcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC

ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (RT inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)

Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy-thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-La Roche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies

IMMUNO-MODULATORS

Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
FP-21399	Fuki ImmunoPharm	blocks HIV fusion with CD4+ cells

Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoeschst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-La Roche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS

Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

Drug Name	Manufacturer	Indication
Clindamycin with Primaquine	Pharmacia Upjohn	PCP

Fluconazole	Pfizer	cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		antibacterial
Trimethoprim/sulfa		antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine isethionate for inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc	cryptosporidial diarrhea
Intraconazole-R51211	Janssen Pharm.	histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP

OTHER

Drug Name	Manufacturer	Indication
Daunorubicin	NeXstar, Sequus	Karposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia

Megestrol Acetate	Bristol-Myers Squibb	treatment of anorexia assoc. w/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	diarrhea and malabsorption related to AIDS

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments of with a compound of the present invention and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. The preparation of ddC, ddI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4)

zidovudine and lamivudine and 141W94 and 1592U89; (5) zidovudine and lamivudine.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-

propylmethylcellulose, sodium alginate, polyvinyl- pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or

gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of The present invention are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

In the treatment or prevention of conditions which require chemokine receptor modulation an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range the dosage may be 0.005 to 0.05, 0.05 to 0.5 or 0.5 to 5.0 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0. 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made from known procedures or as illustrated. Substituted purines may be prepared as disclosed in US 5,057,517; imidazo(1.2-a)pyrazinyl, as disclosed in US 4,242,344; (1,2,4)-triazolo(1.5-a)pyrazinyl as disclosed in *J. Org. Chem*, **1974**, *39*, 2143 and *J.C.S. Perkin I*, **1980**, *506*; 1,7-naphthyridinyl as disclosed in *J. Org. Chem.* **1963**, *28*, 1753; furo(3.2-c)pyridinyl as disclosed in *J. Heterocyclic Chem.*,

1982 ,*19*, 1207; and substituted 6-H-7,8-dihydro-thiopyrano(3.2-d)pyrimidyl as disclosed in *Arch. Int. Pharmacodyn.* **1986**, 280, pp302-313. As appreciated by those of skill in the art, compounds bearing the substituents R_8 and R_9 may be prepared essentially as described in the Schemes.

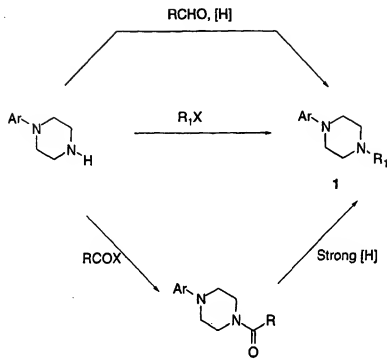
The compounds of the present invention are prepared by alkylating piperazine **1** (R_1 = H) under appropriate conditions (Scheme 1). In one method illustrated by Example 1, Step E, piperazine **1** (R_1 = H) is combined with the appropriate aldehyde and the intermediate imine is reduced to the amine chemically (e.g. using sodium cyanoborohydride) or catalytically (e.g. using hydrogen and palladium on carbon or Raney nickel catalyst) (Scheme 1). The aldehyde needed for this reaction can be prepared by methods generally known in the chemical literature; for the purposes of the present invention the preparation of a representative aldehyde is described in Examples 1 Step A by Hale, J.J.; Finke, P.E.; MacCoss, M. *Bioorganic and Medicinal Chemistry Letters* **1993** *3*, 319-322.

In an alternative embodiment of the present invention, piperazine **1** (R_1 = H) can be alkylated with an alkyl halide or alkyl sulfonate ester (with or without an added base to neutralize the mineral acid or sulfonic acid by-product) to give the desired compound (Scheme 1). The alkyl halide or alkyl sulfonate needed for this reaction can be prepared by methods generally known in the chemical literature; for the purposes of the present invention an aldehyde, prepared as described above, can be reduced to an alcohol with sodium borohydride, diisobutylaluminum hydride or lithium aluminum hydride, and the product alcohol converted to either the alkyl halide using methods described in March J., *Advanced Organic Chemistry*, 3rd ed., John Wiley & Sons, New York, pp. 382-384 (1985), or alkyl sulfonate ester using methods described in March J., *Advanced Organic Chemistry*, 3rd ed., John Wiley & Sons, New York, p. 444 (1985).

In an alternative embodiment of the present invention, 1 (R_1 = H) can be acylated to give the tertiary amide and subsequent reduction with a strong reducing agent (e.g. diborane including borane dimethylsulfide; and, lithium aluminum hydride) will give the desired

compound (Scheme 1). The acylating agent needed for this reaction can be prepared by methods generally known in the chemical literature; for the purposes of the present invention an aldehyde, prepared as described above, can be oxidized using such commonly used reagents as permanganate in acid or silver oxide, and the resulting acid activated as an acid chloride or mixed anhydride which can be used to acylate I. The product amide can be reduced with a strong reducing agent, such as diborane or lithium aluminum hydride, to give the tertiary amine.

SCHEME I

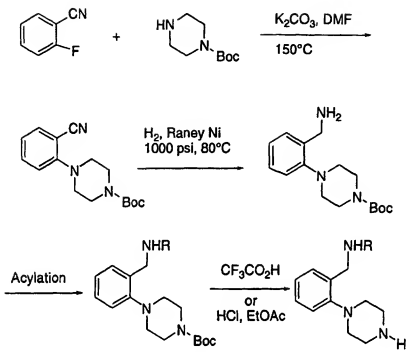


Optionally, Compound 1 formed in the alkylation step may be further modified in subsequent reactions. In one illustration of such an approach, the piperazine fragment may contain a nitro group, which is reduced to the amine after the coupling step. The resulting amine is further modified by acylation to provide the desired compounds. The piperazine fragment may also contain a protecting group such as a benzyl ester or a t-butyl ester. After reductive amination the protecting group is removed and the resulting acid is further reacted to provide additional analogs. Alternatively, the aldehyde portion may also contain a protecting group such as a t-butoxycarbonyl for an amino function. After reductive amination, the t-butoxycarbonyl group is removed by treatment with a strong acid such as trifluoroacetic acid, formic acid or hydrochloric acid and the resulting amine may be acylated to provide other analogs.

The piperazine starting materials used in the coupling reaction are prepared using methods described in the literature; more specifically as described in Meurer, US 5,057,517; US 4,242,344; *J. Org. Chem*, **1974**, *39*, 2143 and *J.C.S. Perkin I*, **1980**, *506*; *J. Org. Chem.* **1963**, *28*, 1753; *J. Heterocyclic Chem.*, **1982** ,*19*, 1207; *Arch. Int. Pharmacodyn.* **1986**, 280, pp302-313 ; Meurer, L.. C. *et al.*, *J. Med. Chem.*, **1992**, *35*, 3845-3857. Alternatively, the piperazine substrates can be prepared as illustrated in Schemes 2-4.

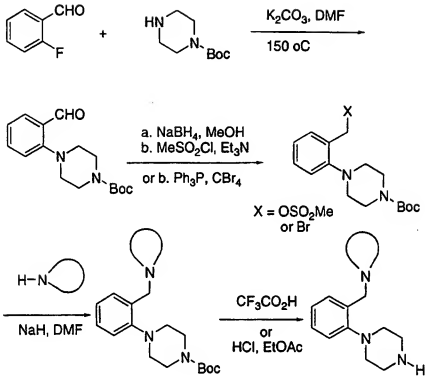
Substituted 4-arylpiperazines can be prepared from appropriate fluorobenzene derivative as shown in Scheme 2. Thus, reaction of 2-fluorobenzonitrile with 1-t-butoxycarbonylpiperazine in the presence of a base such as K_2CO_3 gives 1-t-butoxycarbonyl-4-(2-cyanophenyl)-piperazine. Reduction of the cyano group by hydrogenation in the presence of Raney nickel or by other known methods gives a benzyl amine which can be acylated (Example 1, Step D). The t-butoxycarbonyl protecting group is removed by treatment with trifluoroacetic acid or anhydrous HCl to give a piperazine which can be used in the reductive amination step (Example 1, Step E). Similar reactions using 2-chloro-nitrobenzene in the place of 2-fluorobenzonitrile can provide compounds containing a substituted aniline. Analogs containing a benzoic acid or its derivatives can be prepared by substituting 2-fluorobenzoic acid in this sequence.

SCHEME 2



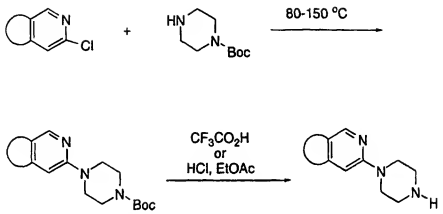
Arylpiperazine derivatives containing heterocyclic substituents can be synthesized as shown in Scheme 3. Reaction between 2-fluorobenzaldehyde and 1-t-butoxycarbonylpiperazine as described above gives 1-t-butoxycarbonyl-4-(2-formylphenyl)-piperazine (Example 9, Step A). Reduction of the aldehyde and treatment of the resulting alcohol with methanesulfonyl chloride gives a mesylate, while treatment of the alcohol with triphenylphosphine and carbon tetrabromide gives the bromide. Displacement of the mesylate by a heterocycle such as imidazole (Example 9, Step C) in the presence of a base and removal of the t-butoxycarbonyl protecting group furnishes piperazine which is used in the coupling reactions described in Scheme I.

SCHEME 3



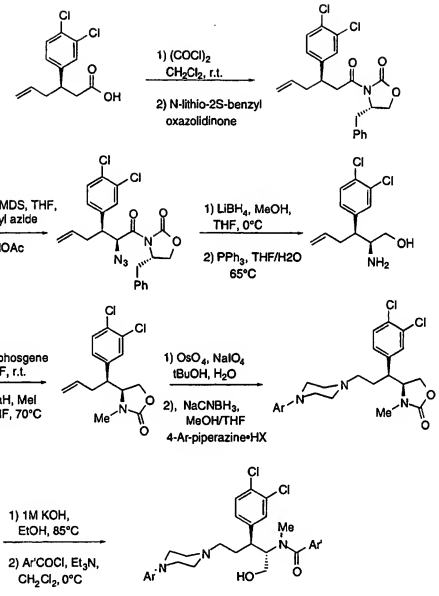
Preparation of piperazines containing a heteroaryl substituent is outlined in Scheme 4. Reaction of 1-t-butoxycarbonyl-piperazine with a chloro substituted heteroaromatic compound such as 8-chloro-1,7-naphthyridine (Example 22, Step A) or 8-chloro-(1,2,4)-triazolo(1,5-a)pyrazine (Example 23, Step A) gives a protected piperazine. Removal of the t-butoxycarbonyl protecting group by treatment with acid provides the piperazine substrate for use in the coupling step.

SCHEME 4



Preparation of hydroxymethyl derivatives of the target compounds is outlined in Scheme 5. The oxazolidinone imide is made from the indicated acid, by formation of the corresponding acid chloride (by treatment with oxalyl chloride or thionyl chloride) and addition of N-lithio 2(S)-benzyl oxazolidinone. The enolate azidation can be accomplished by a variety of methods, such as the procedure of Evans, D. A.; et. al. *J. Am. Chem. Soc.* 1990, *112*, 4011-4030. Reduction of the oxazolidinone moiety can be carried out by a variety of metal hydride reagents (e.g. $LiBH_4$/MeOH, $LiAlH_4$, etc.). The azide is then reduced by treatment with PPh_3/H_2O or $NaBH_4$. Formation of the cyclic carbamate is accomplished by literature methods; i.e. phosgene, triphosgene or carbonyl diimidazole. The target compounds are prepared by oxidative cleavage of the olefin to the aldehyde followed by reductive amination with an amine salt as described for Scheme 1. In one method illustrated by Example 48, the aldehyde is reductively aminated with a heteroaryl substituted aryl piperazine to afford the target precursors. Hydrolysis of the cyclic carbamate under basic conditions (for example, potassium hydroxide in ethanol at elevated temperature) followed by selective amide formation at 0°C by combining with an active acylating agent derived from an aryl carboxylic acid (for example, an aroyl chloride) gives the a-hydroxy-methyl amides.

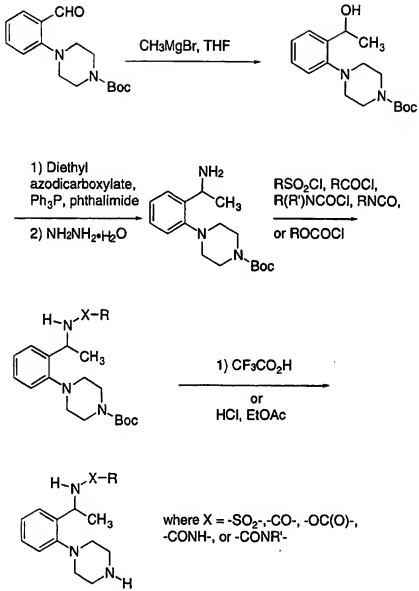
SCHEME 5


1) (COCl)2
CH2Cl2, r.t.
2) N-lithio-2S-benzyl oxazolidinone
KHMDS, THF, trisyl azide
HOAc
1) LiBH4, MeOH, THF, 0°C
2) PPh3, THF/H2O 65°C
1) triphosgene THF, r.t.
2) NaH, MeI DMF, 70°C
1) OsO4, NaIO4 tBuOH, H2O
2), NaCNBH3, MeOH/THF 4-Ar-piperazine•HX
1) 1M KOH, EtOH, 85°C
2) Ar'COCl, Et3N, CH2Cl2, 0°C

Preparation of piperazines containing a heteroaryl substituent on a branched side chain is outlined in Scheme 6. Reaction of the 2-piperazinyl-benzaldehyde derivative whose synthesis is described in Scheme 3 with a carbon nucleophile such as a Grignard reagent, for example methyl magnesium bromide, provides the corresponding benzylic alcohol. Conversion to the benzylic amine can be carried out by treatment of the alcohol with potassium phthalimide in the presence of diethyl azodicarboxylate and triphenyl phosphine, to provide the benzylic N-phthalimido derivative. Heating with hydrazine hydrate then gives the free primary amine. Conversion to the corresponding benzylic amine can also be carried out by activation of the hydroxyl group with a alkyl- or arylsulfonyl chloride, such as p-toluenesulfonyl chloride, to give a benzylic sulfonate ester. The sulfonate ester is then displaced with ammonia or a primary or secondary amine. Alternatively, the sulfonate ester can be displaced with a suitable salt of the azide anion, such as sodium azide, zinc azide, or tetrabutylammonium azide, and the resulting alkyl azide can be reduced to the primary amine with hydrogen gas in the presence of a suitable catalyst, such as 5% palladium on carbon. Alternatively, the alkyl azide can be reduced by treatment with triphenyl phosphine followed by hydrolysis to provide the primary amine.

The benzylic amine can then be derivatized with a number of electrophilic reagents, such as alkyl or aryl sulfonyl chlorides, carboxylic acid chlorides, carboxylic acid anhydrides, alkyl chloroformates, carbamyl chlorides or alkyl or aryl isocyanates to provide sulfonamides, carboxamides, ureas, or carbamates. These intermediates can then be deprotected under acidic conditions to remove the Boc group to provide the free piperazines for use in the coupling reactions described in Scheme I.

SCHEME 6


CHO
N
N
Boc
CH3MgBr, THF
OH
CH3
1) Diethyl azodicarboxylate, Ph3P, phthalimide
2) NH2NH2•H2O
NH2
RSO2Cl, RCOCl, R(R')NCOCl, RNCO, or ROCOCl
H-N-X-R
1) CF3CO2H
or
HCl, EtOAc
where X = -SO2-,-CO-, -OC(O)-, -CONH-, or -CONR'-

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

EXAMPLE 1

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methylamino))butyl)-4-((2-acetylaminomethyl)phenyl)-piperazine

Step A: 3-((S)-(3,4-Dichlorophenyl))-4-((3,5-dimethylbenzoyl)methylamino)-butanal

To a suspension of 4.81 g (32 mmol) of 3,5-dimethyl-benzoic acid in 30 mL of CH_2Cl_2 and 7 drops of DMF was added 3.3 mL (38 mmol) of oxalyl chloride. After stirring for 1 h all the solids were dissolved and gas evolution had stopped. The solution was concentrated and the residual acid chloride was dissolved in 20 mL of CH_2Cl_2. This solution was added to a solution of 7.2 g (29 mmol) of 3-(S)-(3,4-dichlorophenyl)-4-methylamino-1-pentene (prepared as described by J. Hale *et al.*, *Bioorganic and Medicinal Chemistry Letters*, **1993**, *3*, 319-322) in 50 mL of CH_2Cl_2 and 5.3 mL (38 mmol) of triethylamine (Et_3N) with cooling in an ice bath. The ice bath was removed after 5 min and stirring was continued for 1 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water, 1.2 N HCl, saturated $NaHCO_3$ and brine. The solution was dried over Na_2SO_4 and concentrated to give 11.98 g of residual oil. ^1H NMR ($CDCl_3$, ppm ranges are given because of amide rotamers and line broadening) 2.26 (s, 6 H), 2.1-3.9 (m, 8 H), 4.9-5.1 (m, 2 H), 5.4-5.7 (m, 1 H), 6.5 -7.4 (m, 6 H).

The residue was dissolved in 45 mL of acetone, 15 mL of t-butanol and 15 mL of water. To this solution 0.75 mL of osmium tetroxide (4% solution in water) and 3.63 g (31 mmol) of 4-methylmorpholine N-oxide were added. After stirring for 18 h, the reaction was quenched with approximately 30 mL of 10% aqueous Na_2SO_3 and concentrated to 25% of the original volume. The residue

was partitioned between water and 1:1 ether (Et_2O), ethyl acetate (EtOAc), the layers were separated and the aqueous layer was reextracted with Et_2O:EtOAc. Each organic layer was washed with water, brine and dried by filtering through Na_2SO_4. The combined filtrate was concentrated to afford the crude diol.

A solution of the diol in 60 mL of tetrahydrofuran (THF) and 20 mL of water was treated with 6.63 g (31 mmol) of sodium periodate. After stirring for 2 h, the reaction was diluted with Et_2O:EtOAc and washed with water and brine. The organic layer was dried (Na_2SO_4) and the filtrate was concentrated. The residue was purified by prep LC using 30% EtOAC/hexane to furnish 7.86 g (72% yield for three steps) of the title compound as a light yellow solid. ^1H NMR ($CDCl_3$, ppm ranges are given because of amide rotamers and line broadening) δ 2.27 (s, 6 H), 2.6-3.9 (m, 8 H), 6.5-7.5 (m, 6 H), 9.73 (s, 1 H).

Step B: 1-t-Butoxycarbonyl-4-(2-cyano)phenyl-piperazine

To a 30ml DMF solution of t-butylpiperazine carboxylate 10g (53.7mmol) and o-fluorobenzonitrile 4.34g (35.8mmol) were added potassium carbonate 22.26 g (161 mmol) and copper powder 230mg (3.6mmol). The reaction mixture was stirred at 150 °C in an oil bath overnight. After cooling to rt, the reaction mixture was concentrated reduced pressure. The residual material was suspended in EtOAc and was filtered through a pad of celite. The filtrate was washed with sat NH_4Cl aq. solution, dried over anhydrous Na_2SO_4, filtered, concentrated, chromatographed on silica gel column eluting with Hexanes : EtOAc = 10:1 to 7:1 to give 7.84g of the title compound. ^1H-NMR (400MHz $CDCl_3$) δ 1.46(9H,s), 3.13(4H, m), 3.61(4H, m), 6.99-7.04(2H, s), 7.46-7.58(2H,s).

Step C: 1-t-Butoxycarbonyl-4-(2-aminomethyl)phenyl-piperazine

1-t-Butoxycarbonyl-4-(2-cyano)phenyl-piperazine 3g (10.4mmol) was dissolved in EtOH (65ml) and liq. NH_3 (13ml), and was hydrogenated in a bomb (H_2 1000psi, 80° C, 36hr). The solvent was then

removed under reduced pressure to give the title compound. This material was used in step D below without further purification.

Step D: 4-(2-(Acetylaminomethyl)phenyl)-piperazine

A solution of 0.258 g (0.89 mmol) of 4-(2-aminomethyl)-phenyl-1-t-butoxycarbonylpiperazine (from Step C above) in 3 mL of CH_2Cl_2 was treated with 0.075 mL (1.06 mmol) of acetyl chloride and 0.15 mL (1.07 mmol) of Et_3N. After stirring for 20 min the reaction mixture was diluted with CH_2Cl_2 and washed with water, saturated $NaHCO_3$, brine and dried over Na_2SO_4. The filtrate was concentrated and the residue was treated with 10 drops of anisole and 2 mL of cold TFA. The solution was stirred in an ice bath for 1 hr, then concentrated. The residue was partitioned between CH_2Cl_2 and dilute NaOH. The organic layer was washed with brine, dried and the filtrate was concentrated to furnish 0.198 g (96%) of the title compound which was used in the next step without purification. ^1H NMR ($CDCl_3$) δ 2.0 (s, 3 H), 2.90 (m, 4 H), 3.02 (m, 4 H), 4.52 (AB, 2 H), 6.55 (br s, 1 H), 6.85-7.4 (m, 4 H).

Step E: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(2-(acetylaminomethyl)phenyl)-piperazine

To a solution of 0.12 g (0.32 mmol)of 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dimethylbenzoyl)methylamino)butanal (Step A) in 1 mL of MeOH were added 0.099 g (0.42 mmol) of 4-(2-acetylaminomethyl)phenyl-piperazine (Step D), 0.3 g of powdered 4 Å molecular sieves and 20 uL of acetic acid. After stirring the mixture for 1.5 h a solution of 0.063 g (1 mmol) of $NaCNBH_3$ in 3 mL of THF was added. Some gas evolution was observed. After 1 h when the reaction was complete by TLC the mixture was filtered through a pad of celite, the reaction flask and the pad were rinsed with MeOH. The filtrate was concentrated to approximately 2 mL and the residue was diluted with Et_2O:EtOAc. The Et_2O:EtOAc solution was washed with water, brine and dried over Na_2SO_4. The filtrate was concentrated and the residue was purified by prep TLC using 88:10:2 EtOAc:MeOH:Et_3N to isolate

0.163 g (86%) of the title compound as a white foam. ^{1}H NMR ($CDCl_3$, ppm ranges are given because of amide rotamers and line broadening) δ 1.98 (s, 3 H), 1.5-3.9 (m, 18 H), 2.27 (s, 6 H), 4.48 (AB, 2 H), 6.3-6.5 (br, 1 H), 6.6-7.5 (m, 10 H).

EXAMPLE 2

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-(2-(acetylaminomethyl)phenyl)-piperazine

Step A: 3-((S)-(3,4-Dichlorophenyl))-4-((3,5-dichlorobenzoyl)methylamino)-butanal

The title compound was prepared following the procedures described in Example 1, Step A but using 3,5-chlorobenzoyl chloride in the place of freshly prepared 3,5-dimethylbenzoyl chloride. ^{1}H NMR ($CDCl_3$, ppm ranges are given because of amide rotamers and line broadening) δ 2.6-3.9 (m, 8 H), 6.7-7.5 (m, 6 H), 9.7 (s, 1 H).

Step B: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-(2-acetylaminomethylphenyl)-piperazine

The title compound was prepared by the procedure described in Example 1, Step E by substituting 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dichlorobenzoyl)methylamino)butanal as the aldehyde component. Mass Spectrum (CI) 637 ($^{37}Cl + ^{35}Cl$ isotope), 635 ($^{35}Cl + ^{35}Cl$ isotope).

The compounds in Examples 3-8 were prepared by reacting the requisite piperazine with either 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dimethylbenzoyl)methylamino)butanal (Example 1, Step A) or 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dichlorobenzoyl)methylamino) butanal (Example 2, Step A) according to the procedure of Example 1, Step E. The piperazine substrates were synthesized by the method of Example 1, Step D by substituting the appropriate acylation reagent.

EXAMPLE 3

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methylamino))butyl)-4-((2-methylaminocarbonylaminomethyl)phenyl)-piperazineMass Spectrum (CI) 612 (^{37}Cl + ^{35}Cl isotope), 610 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 4

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methylamino))butyl)-4-((2-dimethylaminocarbonylaminomethyl)phenyl)-piperazineMass Spectrum (CI) 626 (^{37}Cl + ^{35}Cl isotope), 624 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 5

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-methylsulfonylaminomethylphenyl)-piperazine
Mass Spectrum (CI) 633 (^{37}Cl + ^{35}Cl isotope), 631 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 6

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-((2-methylaminocarbonylaminomethyl)phenyl)-piperazine
Mass Spectrum (CI) 652 (^{37}Cl + ^{35}Cl isotope), 650 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 7

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-((2-dimethylaminocarbonylaminomethyl)phenyl)-piperazine
Mass Spectrum (CI) 668 (^{37}Cl + ^{35}Cl isotope), 666 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 8

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-(2-methylsulfonylaminomethylphenyl)-piperazine
Mass Spectrum (CI) 675 ($^{37}Cl + {}^{35}Cl$ isotope), 673 ($^{35}Cl + {}^{35}Cl$ isotope).

EXAMPLE 9

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(2-((1'-imidazolyl)methyl)phenyl)-piperazine

Step A: 1-t-Butoxycarbonyl-4-(2-formylphenyl)-piperazine

To a solution of 1 g (8 mmol) of 2-fluorobenzaldehyde in 14 mL of DMF was added 2.25 g (12.1 mmol) of t-butyl 1-piperazine-carboxylate. The resulting solution was treated with 50 mg (0.8 mmol) of copper powder and 5.1 g (36.3 mmol) of ground K_2CO_3 and the suspension was heated to 150°C in a sealed tube. After 18 h, the reaction was cooled and the contents of the tube were partitioned between water and EtOAc. The aqueous layer was reextracted with EtOAc and the organic layers were combined. The organic layer was washed with water, brine and dried. The filtrate was concentrated and the residue was chromatographed on a flash column with 12% EtOAc-Hexane to furnish 1.15 g (49%) of 1-t-butoxycarbonyl-4-(2-formyl-phenyl)-piperazine. ^1H NMR ($CDCl_3$) δ 1.44 (s, 9 H), 3.0 (m, 4 H), 3.59 (m, 4 H), 7.0-7.8 (m, 4 H), 10.31 (s, 1 H).

Step B: 1-t-Butoxycarbonyl-4-(2-hydroxymethylphenyl)-piperazine

A solution of 1.15 g (3.96 mmol) of 1-t-butoxycarbonyl-4-(2-formyl-phenyl)-piperazine in 10 mL of MeOH was treated with 0.15 g (3.96 mmol) of $NaBH_4$. After 2 h the reaction was quenched by adding 1.2 N HCl and the mixture was extracted with EtOAc. The EtOAc solution was washed with water, brine and dried. The filtrate was concentrated to yield 1.1 g (95%) of 1-t-butoxycarbonyl-4-(2-hydroxymethyl-phenyl)-piperazine as a white foam which was used without purification. ^1H NMR ($CDCl_3$) δ 1.24 (s, 9 H), 2.92 (m, 4 H), 3.59 (m, 4 H), 4.84 (s, 2 H), 7.0-7.4 (m, 4 H).

Step C: 1-t-Butoxycarbonyl-4-(2-((1'-imidazolyl)methyl)phenyl)-piperazine

To 0.2 g (0.68 mmol) of 1-t-butoxycarbonyl-4-(2-hydroxymethylphenyl)piperazine in 2 mL of CH_2Cl_2 were added 0.064 mL (0.82 mmol) of methanesulfonyl chloride and 0.11 mL (0.82 mmol) of Et_3N. After stirring for 30 min the reaction was partitioned between water and CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried and concentrated and the residue was dissolved in 1 mL of DMF. This solution was added to a mixture of 51 mg (0.75 mmol) of imidazole in 1 mL of DMF and 18 mg (0.75 mmol) of NaH which had been stirred for 30 min. After heating the reaction mixture for 18 h at 60 °C, it was cooled and partitioned between water and EtOAc. The organic layer was washed with water, brine, dried and the filtrate was concentrated. The residue was chromatographed using 5% MeOH-CH_2Cl_2 to isolate 0.096 g (41%) of 1-t-butoxycarbonyl-4-(2-((1'-imidazolyl)methyl)-phenyl)-piperazine. ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.74 (m, 4 H), 3.53 (m, 4 H), 5.2 (s, 2 H) 6.89 (s, 1 H), 7.0-7.4 (m, 5 H), 7.54 (s, 1 H).

Step D: 4-(2-((1'-Imidazolyl)methyl)phenyl)-piperazine

Cold TFA (1 mL) and 0.1 mL of anisole were added to 0.096 g (0.28 mmol) of 1-t-butoxycarbonyl-4-(2-((1'-imidazolyl)-methyl)phenyl)-piperazine. The bath was removed and the mixture stirred for 1 h while it warmed to room temperature. The reaction mixture was concentrated and the residue was partitioned between CH_2Cl_2 and dilute NaOH. The CH_2Cl_2 layer was washed with brine, dried and concentrated to give 0.047 g (69%) of the title compound which was used without purification. ^1H NMR ($CDCl_3$) δ 2.78 (m, 4 H), 3.02 (m, 4 H), 5.2 (s, 2 H), 6.89-7.4 (m, 6 H), 7.54 (s, 1 H).

Step E: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethyl benzoyl(methylamino))butyl)-4-(2-((1'-imidazolyl)-methyl)-phenyl)piperazine

The reaction between 47 mg (0.19 mmol) of 4-(2-((1'-imidazolyl) methyl)phenyl)-piperazine and 92 mg (0.24 mmol) of 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dimethylbenzoyl)methylamino)-butanal

according to the method of Example 1, Step E furnished 55 mg (47%) of the title compound. ^{1}H NMR ($CDCl_3$, ppm ranges are given because of amide rotamers and line broadening) δ 1.5-3.9 (m, 18 H), 2.27 (s, 6 H), 5.14 (s, 2 H), 6.6-7.6 (m, 13 H). Mass Spectrum (CI) 606 (^{37}Cl + ^{35}Cl isotope), 604 (^{35}Cl + ^{35}Cl isotope).

The compounds in Examples 10-14 were prepared by the procedure of Example 9 substituting the requisite heterocycle for imidazole in Step C and carrying out Step E with either 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dimethylbenzoyl)methyl-amino)-butanal (from Example 1, Step A) or 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dichlorobenzoyl)methyl-amino)-butanal (from Example 2, Step A).

EXAMPLE 10

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-(2-(1'-(1',2',4'-triazolyl)methylphenyl)-piperazine
Mass Spectrum (CI) 647 (^{37}Cl + ^{35}Cl isotope), 645 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 11

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(2-(1'-(1',2',4'-triazolyl)methylphenyl)-piperazine
Mass Spectrum (CI) 607 (^{37}Cl + ^{35}Cl isotope), 605 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 12

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(2-(1'-(1',2',3',4'-tetrazolyl)methylphenyl)-piperazine
Mass Spectrum (CI) 608 (^{37}Cl + ^{35}Cl isotope), 606 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 13

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(2-(3'-pyridyloxy)methylphenyl)-piperazine

The title compound was synthesized by the method of Example 9 by substituting 3-hydroxypyridine for imidazole in Step C.
Mass Spectrum (CI) 633 (^{37}Cl + ^{35}Cl isotope), 631 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 14

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-(1'-(2'(1'H)-pyridone)methylphenyl)-piperazine

The title compound was prepared according to Example 9 and using 2-hydroxypyridine in Step C. Mass Spectrum (CI) 633 (^{37}Cl + ^{35}Cl isotope), 631 (^{35}Cl + ^{35}Cl isotope).

EXAMPLE 15

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-methylphenyl)piperazine

Step A: 3-(S)-(3,4-Dichlorophenyl)-4-(N-(3,5-dimethylbenzoyl) methylamino)butanol

To a solution of 3-((S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethylbenzoyl)methylamino)butanal (2.5 g; from Example 1, Step A) in 35 mL of methanol at 0°C was added portionwise over 5 min sodium borohydride (400 mg). After stirring for 1 h at r.t., the reaction was slowly quenched with 2 N HCl and extracted twice with ethyl acetate. The organic layers were washed with brine, dried (Na_2SO_4), combined and evaporated to give 2.5 g (100%) of a crude oil. Residual water and methanol were removed by concentration from a portion of isopropyl acetate.

Step B: 4-Bromo-2-(S)-(3,4-dichlorophenyl)-1-(N-(3,5-dimethylbenzoyl)methylamino)butane

To a solution of crude 3-(S)-(3,4-dichlorophenyl)-4-(N-(3,5-dimethylbenzoyl)methylamino)butanol (2.5 gm) from Step A in 30 mL of acetonitrile was added 3.5 g (8.25 mmol) of triphenylphoshine dibromide. The reaction was stirred at r.t. for 16 h and was then partitioned between ethyl ether and water. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was flash chromatograghed with a solvent gradient of 25-40% EtOAc/Hexanes to give 2.6 g (89% from

Step A) of oil which solidified on standing. Mass Spectrum (ESI 80/20 MeCN/H_2O, 0.01% TFA) M+H = 441, 443, 445($^{35,37}Cl$, ^{79}Br,^{81}Br-isotope).

Step C: (3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(2-methylphenyl)piperazine

A solution of 4-bromo-2-(S)-(3,4-dichlorophenyl)-1-(N-(3,5-dimethylbenzoyl)methylamino)butane prepared in Step B (50 mg), N,N-diisopropylethylamine (40 ul) and 1-(2-methylphenyl)-piperazine (40 mg) in 0.5 mL of acetonitrile was heated in a tightly capped vial at 50°C for four days. The solvent was evaporated and the residue was purified on a 1000 um silica gel prep plate (4% MeOH/CH_2Cl_2)) to furnish 30 mg (50%) of the title compound as a white foam.
Mass Spectrum (CI/NH_3) M+H = 537,539 ($^{35,37}Cl$-isotope).

EXAMPLE 16

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(phenyl)piperazine

Following essentially the same procedure as in Example 15 but substituting 1-phenylpiperazine (35 mg), 30 mg (51%) of the title compound was prepared.
Mass Spectrum (CI/NH_3) M+H = 523, 525 ($^{35,37}Cl$-isotope).

EXAMPLE 17

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(9-(2-fluoroethyl)-2-methoxy-purin-6-yl) piperazine

A mixture of 4-bromo-2-(S)-(3,4-dichlorophenyl)-1-(N-(3,5-dimethylbenzoyl)methylamino)butane prepared in Example 15, Step B above (43.5 mg), N,N-diisopropylethylamine (68 ul) and 9-(2-fluoroethyl)-2-methoxy-6-(1-piperazinyl)purine dihydrochloride (69 mg; prepared according to D.B. Johnston, M. MacCoss, S. Marburg, L. Meurer, and R. L. Tolman; U.S. Patent # 5,057,517) in 0.5 mL of acetonitrile was heated in a tightly capped vial at 50°C for four days. The solvent was evaporated and the residue was purified on a 1000 um silica gel prep

plate (93:5:2 ethyl acetate:methanol:triethylamine) to furnish 32.5 mg of the title compound as a white foam.
Mass Spectrum (CI/NH_3) M+H = 642, 644(^{35,37}Cl-isotope).

The compounds in Examples 18-30 were (unless otherwise stated) prepared from 4-bromo-2-(S)-(3,4-dichlorophenyl)-1-(N-(3,5-dimethylbenzoyl)methylamino)butane (prepared in Example 15, Step B) and the appropiate piperazine derivatives by essentially the same procedure as in Example 17.

EXAMPLE 18

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(9-(2-methoxymethyl)-2-methoxy-purin-6-yl) piperazine

The starting piperazine was prepared according to D.B. Johnston, M. MacCoss, S. Marburg, L. Meurer, and R. L. Tolman; U.S. Patent # 5,057,517. Mass Spectrum (CI/NH_3) M+H = 640, 642 (^{35,37}Cl-isotope).

EXAMPLE 19

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(9-methyl-purin-6-yl)piperazine

The starting piperazine was prepared according to D.B. Johnston, M. MacCoss, S. Marburg, L. Meurer, and R. L. Tolman; U.S. Patent # 5,057,517. Mass Spectrum (CI/NH_3) M+H = 580, 582 (^{35,37}Cl-isotope).

EXAMPLE 20

1-(3-((S)-(4-Chlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(9-methyl-purin-6-yl)piperazine

The title compound was prepared from 4-bromo-2-(S)-(4-chlorophenyl)-1-(N-(3,5-dimethylbenzoyl)methylamino)butane (prepared

by analogy to 4-bromo-2-(S)-(3,4-dichlorophenyl)-1-(N-(3,5-dimethylbenzoyl)methylamino)butane in Example 15, Steps A and B) and the requisite piperazine, which was prepared according to D.B. Johnston, M. MacCoss, S. Marburg, L. Meurer, and R. L. Tolman; U.S. Patent # 5,057,517. Mass Spectrum (CI/NH_3) M+H = 546,548 (^{35,37}Cl-isotope).

EXAMPLE 21

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(6-methyl-imidazo(1,2-a)pyrazin-1-yl) piperazine

The starting piperazine was prepared according to L.C. Meurer, R.L. Tolman, E.W. Chapin, R. Saperstein, P.P. Vicario, M.F. Zrada and M. MacCoss, *J. Med. Chem.* **1992**, *35*, 3845-3857. Mass Spectrum (CI/NH_3) M+H = 579, 581 (^{35,37}Cl-isotope).

EXAMPLE 22

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(1,7-naphthyridin-8-yl)piperazine

Step A: 8-(1-(4-t-Butyloxycarbonyl)piperazinyl)-1,7-naphthyridine.

To a solution of 1.56 g(9.48 mml) of 8-chloro-1,7-naphthyridine (*J. Org. Chem.* **1963**, *28*, 1753) in 100 mL of isoamyl alcohol was added 1-(t-butyloxycarbonyl)piperazine (6.36g, 34.15mmol). This solution was heated under reflux, under nitrogen for 2hr and then the reaction mixture was evaporated to dryness and the residue was dissolved in CH_2Cl_2 (100mL) and 10% aq. Na_2CO_3 (100mL). After shaking, the layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 x 100mL) and the pooled organic layers were dried (over $MgSO_4$), filtered, and evaporated to dryness. This oily residue was dissolved in a little CH_2Cl_2, absorbed onto silica gel 60, and chromatographed on a dry-packed silica gel 60 column (3.5 x 20.5 cm) developed with EtOAc : hexanes (1 : 3). Fractions containing the desired product were pooled and evaporated to dryness to give a thick yellow

syrup which crystallized on standing. Yield 2.78g (8.84mmol, 93% yield). Mass Spec. showed M^+ at m/e 314.
Analysis calculated for $C_{17}H_{22}N_4O_2$ (314): C, 64.95; H, 7.05; N, 17.82, Found: C, 64.53; H, 6.71; N, 17.66.

Step B: 8-(1-Piperazinyl)-1,7-naphthyridine dihydrochloride 8-(1-(4-t-Butyloxycarbonyl)piperazinyl)-1,7-naphthyridine, prepared as described above (1.02g, 3.24mmol), was dissolved in abs. EtOH (10mL) and ethanolic HCl (8mL) was added. This solution was left at room temperature for 10min and then was evaporated to dryness slowly under a nitrogen stream. This residue was evaporated to dryness from H_2O and then from EtOH to give a white residue that was triturated under EtOH, filtered, and dried at 45°C *in vacuo* to give 0.71g (2.47mmol, 76% yield) of the title compound.Analysis calculated for $C_{12}H_{16}N_4Cl_2$ (287.19): C, 50.19; H, 5.62; N, 19.51, Found: C, 49.89; H, 5.51; N, 19.28.

Step C: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(1,7-naphthyridin-8-yl)piperazine.

The title compound was prepared by reacting 4-bromo-2-(S)-(3,4-dichlorophenyl)-1-(N-(3,5-dimethylbenzoyl)methylamino)-butane and 8-(1-piperazinyl)-1,7-naphthyridine dihydrochloride according to the procedure of Example 17. Mass Spectrum (CI/NH_3) M+H = 576, 578 ($^{35,37}Cl$-isotope).

EXAMPLE 23

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(1,2,4-triazolo(1,5-a)pyrazin-8-yl)piperazine.

Step A: 8-(1-(4-t-Butyloxycarbonyl)piperazinyl)-(1,2,4)-triazolo(1,5-a)pyrazine

8-Chloro-(1,2,4)-triazolo(1,5-a)pyrazine (*J. Org. Chem*, 1974, *39*, 2143 and *J.C.S. Perkin I*, 1980, 506) (1.62g, 10.41mmol) and 1-(t-butyloxycarbonyl)piperazine (8.15g, 43.76mmol, prepared as described in *J. Het. Chem.* 1990 *27*, 1559) were mixed and dissolved in EtOH (75mL).

This solution was heated under reflux, under nitrogen, for 2hr and then the mixture was evaporated to dryness under reduced pressure and the residue was dissolved in i-pentyl alcohol (75mL) and the reflux continued for 4hr. The reaction mixture was cooled and evaporated to dryness to give a yellow syrupy residue that was dissolved in CH_2Cl_2 (60mL) and 10% aq. Na_2CO_3 (60mL). After shaking, the layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 x 60mL) and the pooled organic layers were dried (over $MgSO_4$), filtered, and evaporated to dryness. The residue was dissolved in a little CH_2Cl_2, absorbed onto silica gel 60, and chromatographed on a dry-packed silica gel 60 column (3 x 36 cm) developed with EtOAc : hexanes (1 : 3). Fractions containing the required product were pooled and evaporated to dryness to give 2.15g (7.04mmol, 67% yield) of the title compound. Mass Spec. showed M^+ at m/e 304. Analysis calculated for $C_{14}H_{20}N_6O_2$ (304.35): C, 55.25; H, 6.62; N, 27.61, Found: C, 55.18; H, 6.53; N, 27.30

Step B: 8-(1-Piperazinyl)-(1,2,4)-triazolo(1,5-a)pyrazine dihydrochloride

8-(1-(4-t-Butyloxycarbonyl)piperazinyl)-(1,2,4)-triazolo(1,5-a)pyrazine (1.18g, 3.86mmol), was dissolved in EtOH : EtOAc (1 : 1, 40mL) with warming and ethanolic HCl (10mL) was added. Precipitation occurred immediately and the mixture was left at room temperature for $2^1/_2$ hr. The reaction mixture was blown down to dryness under a nitrogen stream and triturated under EtOH/EtOAc/Et_2O and the white solid so obtained was filtered off and dissolved in CF_3CO_2H (15mL) and then evaporated under a stream of nitrogen over a period of $1^1/_2$ hr. The residue so obtained was evaporated to dryness twice from H_2O and then dissolved in a little H_2O and passed down a Dowex 1x2 (OH^-form) column (2 x 26 cm) packed and developed in H_2O. Fractions containing the required product were pooled and evaporated to dryness to give 0.78g (3.82mmol, 99% yield) of the title compound as the free base. This was dissolved in EtOH (15mL) with warming and ethanolic HCl was added. Immediate precipitation of the product occurred and this was filtered off after dilution with Et_2O to give

1.00g (3.61mmol, 94% yield overall) of the title compound.Analysis calculated for $C_9H_{14}N_6Cl_2.0.5H_2O$ (286.15):

C, 37.77; H, 5.28; N, 29.37, Found: C, 37.63; H, 5.28; N, 29.23.

Step C: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(1,2,4-triazolo(1,5-a)pyrazin-8-yl)piperazine.

Reaction of 4-bromo-2-(S)-(3,4-dichlorophenyl)-1-(N-(3,5-dimethylbenzoyl)methylamino)butane with 8-(1-piperazinyl)-(1,2,4)-triazolo(1,5-a)pyrazine dihydrochloride as described in example 17 gave the title compound. Mass Spectrum (CI/NH_3) M+H = 566, 568 (^{35,37}Cl-isotope).

EXAMPLE 24

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(5-methyl-pyrid-2-yl)piperazine.

The starting piperazine was prepared according to U.S. Patent # 4,876,256 (1989). Mass Spectrum (CI/NH_3) M+H= 539, 541 (^{35,37}Cl-isotope).

EXAMPLE 25

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-amino-pyrazin-4-yl)piperazine.

Step A: 2-Amino-4-(1-piperazinyl)pyrimidine dihydrochloride

2-Amino-6-chloro-4-(1-piperazinyl)pyrimidine, prepared as described in *J. Med. Pharm. Chem.*, **5**, 558 (1962), (1.07g, 5mmol) was suspended in EtOH (100mL) and heated and sonicated to effect maximum dissolution. MgO (0.75g) was added followed by 5% Pd on C (0.48g). The mixture was hydrogenated for 18 3/4 hr at room temperature and then was warmed and filtered while hot through a Celite pad, washing the pad well with hot EtOH. The filtrate was evaporated to a white solid residue (1.14g, quantitative yield). An analytical sample was

obtained by conversion to the dihydrochloride salt using ethanolic HCl in the usual fashion. Anal. Calc. for $C_8H_{15}N_5Cl_2.0.1H_2O$ (253.94): C 37.84; H 6.03; N 27.58; Cl 27.92, Found: C 38.21; H 5.90; N 27.15; Cl 28.02.

Step B: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-amino-pyrazin-4-yl)piperazine

Reaction of 4-bromo-2-(S)-(3,4-dichlorophenyl)-1-(N-(3,5-dimethylbenzoyl)methylamino)butane with 2-amino-4-(1-piperazinyl)pyrimidine dihydrochloride according to the procedure given in Example 17 gave the title compound. Mass Spectrum (CI/NH_3) M+H = 541, 543 (^{35,37}Cl-isotope).

EXAMPLE 26

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(furo(2,3-c)pyrid-4-yl))piperazine

Step A: 7-(1-(4-t-Butyloxycarbonyl)piperazinyl)furo(2,3-c)pyridine

7-Chlorofuro(2,3-c)pyridine, prepared as described in *J. Heterocyclic Chem.*, **19**, 1207 (1982), (1.54g, 10mmol) and 1-(t-butyloxycarbonyl)piperazine (7.45g, 40mmol) were mixed and heated at 180°C under nitrogen for 3hr, cooled, and the residue was partitioned between $CHCl_3$ (50mL) and 5% aqueous $NaHCO_3$ (30mL). The organic phase was dried and evaporated to dryness and the oil so obtained was dissolved in $CHCl_3$ and chromatographed on a column of silica gel, developed initially with $CHCl_3$ and then with hexanes : EtOAc (3 : 1). Fractions containing the required product were pooled and evaporated to dryness to give 1.90g of the title compound.anal. Calc. for $C_{14}H_{22}N_4O_3$ (294.36): C 57.12; H 7.53; N 19.03 Found: C 56.77; H 7.24; N 19.16.

Step B: 7-(Piperazinyl)furo(2,3-c)pyridine trifluoroacetate

The title compound was prepared by deprotection of 7-(1-(4-t-butyloxycarbonyl)piperazinyl)furo(2,3-c)pyridine with trifluoroacetic acid

in methylene chloride in the presence of anisole. The crude product was used immediately in Step C.

Step C: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(furo(2,3-c)pyrid-4-yl))piperazine.

Reaction of 4-bromo-2-(S)-(3,4-dichlorophenyl)-1-(N-(3,5-dimethylbenzoyl)methylamino)butane with 7-(piperazinyl)furo(2,3-c)pyridine trifluoroacetate according to the procedure given in example 17 gave the title compound. Mass Spectrum (CI/NH_3) M+H = 565, 567 (^{35,37}Cl-isotope).

EXAMPLE 27

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-amino-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine

The starting piperazine was prepared according to Kunch, Y., Iguchi, A., Gotch, M., Nomura, T., Shibata, M., Sakamoto, N. *Arch. Int. Pharmacodyn.* **1986**, *280*, 302-313. Mass Spectrum (CI/NH_3) M+H = 613, 615 (^{35,37}Cl-isotope).

EXAMPLE 28

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-methyl-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine

The title compound was prepared by reaction of 4-bromo-2-(S)-(3,4-dichlorophenyl)-1-(N-(3,5-dimethylbenzoyl)methylamino)-butane (Example 15, Steps A and B) and 2-methyl-7,8-dihydro-4-piperazinyl-6H-thiopyrano[3,2-d]pyrimidine (prepared by analogy to the preparation of 2-amino-7,8-dihydro-4-piperazinyl-6H-thiopyrano[3,2-d]pyrimidine, as described in Ohno et al, UK Patent Application GB 2,119,368 A, 16 Nov. 1983, by substituting acetamidine hydrochloride for guanidine carbonate

in the reaction with ethyl 3-oxotetrahydrothiapyran-2-carboxylate) according to the procedure given in Example 17. Mass Spectrum (CI/NH_3) M+H = 612, 614 (^{35,37}Cl-isotope).

EXAMPLE 29

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-bis(trifluoromethyl)-benzoyl)-(methylamino))butyl)-4-(1,2,4-triazolo(1,5-a)pyrazin-8-yl)piperazine

The title compound was prepared by reaction of 4-bromo-2-(S)-(3,4-dichlorophenyl)-1-(N-(3,5-bis(trifluoromethyl)benzoyl)-methylamino)butane (prepared by analogy to 4-bromo-2-(S)-(3,4-dichlorophenyl)-1-(N-(3,5-dimethylbenzoyl)methylamino)butane in Example 15, Steps A and B) and 8-(1-piperazinyl)-(1,2,4)-triazolo(1,5-a)pyrazine dihydrochloride (prepared in Example 23, Step B) according to the procedure given in Example 17. Mass Spectrum (CI/NH_3) M+H = 674.

EXAMPLE 30

1-(3-((S)-(4-Chlorophenyl))-4-(N-(3,5-bis(trifluoromethyl)benzoyl)-(methylamino))butyl)-4-(1,2,4-triazolo(1,5-a)pyrazin-8-yl)piperazine.

The title compound was prepared by reaction of 4-bromo-2-(S)-(4-chlorophenyl)-1-(N-(3,5-bis(trifluoromethyl)benzoyl)methyl-amino)butane (prepared by analogy to 4-bromo-2-(S)-(3,4-dichlorophenyl)-1-(N-(3,5-dimethylbenzoyl)methylamino)butane in Example 15, Steps A and B) and 8-(1-piperazinyl)-(1,2,4)-triazolo(1,5-a)pyrazine dihydrochloride (prepared in Example 23, Step B) according to the procedure given in Example 17. Mass Spectrum (CI/NH_3) M+H = 640.

EXAMPLE 31

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(2-amino-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine-5-oxide

A solution of 1-(3-((S)-(3,4-dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-amino-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine (13 mg; Example 27) in .5 mL of methanol at 0°C was treated with a solution of 17 mg of oxone in 0.5 mL of water. After three minutes the reaction was quenched with 10% aqueous sodium bisulfite and stirred for five minutes. The mixture was diluted with saturated sodium bicarbonate and extracted twice with dichloromethane. The combined organic layer was washed with brine, dried (Na_2SO_4) and evaporated to a clear oil. Purification on a 1000 um silica gel prep plate (9:1 CH_2Cl_2:MeOH) provided 4.6 mg of product as a white foam. Mass Spectrum (CI/NH_3) M+H = 629, 631(^{35,37}Cl-isotope).

EXAMPLE 32

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-methyl-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine-5-oxide

The title compound was prepared by following essentially the same procedure as in Example 31 but employing 1-(3-((S)-(3,4-dichlorophenyl))-4-(N-(3,5-dimethyl-benzoyl)-(methylamino))butyl)-4-(2-methyl-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine (from Example 28) as starting material. Mass Spectrum (CI/NH_3) M+H = 628, 630 (^{35,37}Cl-isotope).

EXAMPLE 33

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl-(methylamino))butyl)-4-(2-(2'-(tetrazolyl)methyl)phenyl)-piperazine

Step A: 3-((S)-(3,4-Dichlorophenyl))-4-((N-3,5-bis-trifluoromethylbenzoyl)methylamino)-butanal

Following the procedure described in Example 1 step A, 3-((S)-(3,4-dichlorophenyl))-4-((N-3,5-bis-trifluoromethylbenzoyl)-methylamino)-butanal was prepared using 3,5-bis-trifluoromethyl-benzoic acid instead

of 3,5-dimethylbenzoic acid. ^{1}H-NMR (500MHz $CDCl_3$) d2.5-4.0(8H, m), 6.7-8.0(6H, m), 9.78(1H, s).

Step B: 1-t-Butoxycarbonyl-4-(2-bromomethyl)phenyl)-piperazine

To 410mg (1.4mmol) of 1-t-butoxycarbonyl-4-(2-hydroxymethyl)phenyl)-piperazine (prepared in Example 9, Step B) in 12 mL of acetonitrile was added 625 mg (2.38mmol) of triphenylphosphine and 698mg (2.1mmol) of carbon tetrabromide with cooling in an ice-water bath. After the mixture was stirred in a cold room (4°C) for 14hr, the solvent was removed under reduced pressure. The resulting oil was dissolved in EtOAc and water was then added. The phases were separated and the aqueous phase was extracted with two small portions of EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, concentrated, and triturated with hexane. The triphenylphosphine oxide which precipitated was removed by filtration. The filtrate was concentrated to give the title compound, which was used in step C without further purification. ^{1}H-NMR (500MHz $CDCl_3$) δ 1.51(9H. s), 2.94(4H, m), 3.61(4H,s), 4.72(2H,s), 7.1-7.5(4H, m).

Step C: 1-t-Butoxycarbonyl-4-(2-(1'-(tetrazolyl)methyl)phenyl)-piperazine and 1-t-Butoxycarbonyl-4-(2-(2'-(tetrazolyl)methyl)phenyl)-piperazine

To a solution of 294mg (4.2mmol) of 1H-tetrazole in 9ml DMF was added 111mg (4.63mmol) sodium hydride at rt. After stirring for 10min, 9ml of the DMF solution of 1-t-butoxycarbonyl-4-(2-bromomethyl)phenyl)-piperazine prepared in step B was added, and the mixture was stirred in an oil bath at 70° C for 1.5hr. The DMF was then removed under reduced pressure. The resulting material was dissolved in EtOAc and sat. NH_4Cl aq. solution. The organic phase was separated and the aqueous phase was extracted twice with small portions of EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, concentrated, and chromatographed on silica gel eluting with Hexane : EtOAc = 5 : 1 to 1 : 1 to give 144.3mg of 1-t-butoxycarbonyl-4-(2-(2'-(tetrazolyl)methyl)phenyl)-piperazine (higher Rf), and 224.1mg of 1-t-

butoxycarbonyl-4-(2-(1'-(tetrazolyl)methyl)-phenyl)-piperazine (lower Rf). 1-t-Butoxycarbonyl-4-(2-(2'-(tetrazolyl)methyl)phenyl)-piperazine: ^{1}H-NMR (500MHz $CDCl_3$) δ 1.50(9H, s), 2.83(4H, s), 3.58(4H, s), 6.00(2H, s), 7.1-7.4(4H, m), 8.52(1H, s). Mass Spectrum (CI) 345 (M^++1). 1-t-Butoxycarbonyl-4-(2-(1'-(tetrazolyl)methyl)phenyl)-piperazine: ^{1}H-NMR (500MHz $CDCl_3$) δ 1.50(9H, s), 2.80(4H, s), 3.55(4H, s), 5.73(2H, s), 7.1-7.43(4H, m), 8.52(1H, s). Mass Spectrum (CI) 245(M^++H-Boc)

Step D: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(2'-(tetrazolyl)methyl)phenyl)-piperazine

1-t-Butoxycarbonyl-4-(2-(2'-(tetrazolyl)methyl)phenyl)-piperazine was deprotected under the conditions given in Example 9, Step D, and the product was then reacted with 4-bromo-2-(S)-(3,4-dicholorophenyl)-4-(N-3,5-bis-trifluoromethylbenzoyl)methyl-amino)butanal (prepared in step A) following the procedure described in Example 1 step E to give the title compound. MS(CI) 714(M^++H)(^{35}Clx2), 716(^{35}Cl, ^{37}Cl)

EXAMPLE 34

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl-(methylamino))butyl)-4-(2-(1'-(tetrazolyl)-methyl)phenyl)-piperazine

The title compound was prepared as following the procedure in Example 33, Step D using 1-t-butoxycarbonyl-4-(2-(1'-(tetrazolyl)methyl)phenyl)-piperazine prepared in Example 33, Step C. MS(CI) 714(M^++H)(^{35}Clx2), 716(^{35}Cl, ^{37}Cl)

EXAMPLE 35

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl-(methylamino))butyl)-4-(2-(1'-(1', 2', 4'-triazolyl)methyl)phenyl)-piperazine

Step A 1-t-Butoxycarbonyl-4-(2-(1'-(1', 2', 4'-triazolyl)methyl)-phenyl)-piperazine and 1-t-Butoxycarbonyl-4-(2-(4'-(1', 2', 4'-triazolyl)methyl)phenyl)-piperazine

Following the procedure described in Example 33, Step C, the title compounds were prepared using 1,2,4-triazole instead of 1-H tetrazole. 1-t-Butoxycarbonyl-4-(2-(1'-(1', 2', 4'-triazolyl)methyl)-phenyl)-piperazine: ^{1}H-NMR(500MHz CDCl3) δ 1.50(9H, s), 2.81(4H, s), 3.56(4H, s), 5.49(2H, s),7.1-8.1(6H, m). Mass Spectrum (CI) 344(M^++H). 1-t-Butoxycarbonyl-4-(2-(4'-(1', 2', 4'-triazolyl)methyl)phenyl)-piperazine: ^{1}H-NMR(500MHz CDCl3) δ 1.50(9H, s), 2.79(4H, s), 3.56(4H, s), 5.29(2H, s), 7.1-7.42(4H, m), 8.21(2H, s). Mass Spectrum (CI) 344(M^++H).

Step B: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(1'-(1', 2', 4'-triazolyl)methyl)phenyl)-piperazine

According to the procedure described in Example 33, Step D, the title compound was prepared from 1-t-butoxycarbonyl-4-(2-(1'-(1', 2', 4'-triazolyl)methyl)phenyl)-piperazine. Mass Spectrum (CI) 713(M^++H, ^{35}Clx2), 715(M^++H, ^{35}Cl, ^{37}Cl)

EXAMPLE 36

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl-(methylamino))butyl)-4-(2-(4'-(1', 2', 4'-triazolyl)-methyl)-phenyl)-piperazine

According to the procedure described in Example 33, Step D, the title compound was prepared from 1-t-butoxycarbonyl-4-(2-(4'-(1', 2', 4'-triazolyl)methyl)phenyl)-piperazine prepared in Example 35, Step A. Mass Spectrum (CI) 713(M^++H, ^{35}Clx2), 715(M^++H, ^{35}Cl, ^{37}Cl)

EXAMPLE 37

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl-(methylamino))butyl)-4-(2-(1'-(1', 2', 3'-triazolyl)-methyl)-phenyl)-piperazine

Step A: 1-t-Butoxycarbonyl-4-(2-(1'-(1', 2', 3'-triazolyl)methyl)phenyl)-piperazine

The title compound was prepared according to the procedure described in Example 33, Step C using 1,2,3-triazole istead of 1H-tetrazole. ^{1}H-NMR(400MHz CDCl3) δ 1.46(9H, s), 2.78(4H, s), 3.55(4H, s), 5.70(2H, s), 7.05-7,75(6H, s).

Step B 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(1'-(1', 2', 3'-triazolyl)-methyl)-phenyl)-piperazine

Following the procedure described in Example 33, Step D, the title compound was prepared using 1-t-butoxycarbonyl-4-(2-((1', 2', 3'-triazolyl)methyl)phenyl)-piperazine. MS(CI) 713(M^++H, ^{35}Clx2), 715(M^++H, ^{35}Cl, ^{37}Cl)

EXAMPLE 38

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl-(methylamino))butyl)-4-(2-(methanesulfonylaminomethyl)phenyl)-piperazine

Step A: 1-t-Butoxycarbonyl-4-(2-(methanesulfonylaminomethyl)-phenyl)-piperazine

The piperazine synthesized in Example 1, Step C was subjected to the condition described in Example 1 Step D using methanesulfonyl chloride instead of acetyl chloride.

Step B 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(methanesulfonylaminomethyl)phenyl)-piperazine

The piperazine obtained in Step A was reacted with the aldehyde prepared in Example 33, Step A following the conditions described in Example 1, Step E to give the title compound. MS(CI) 739(M^++H)(^{35}Clx2), 741(M^++H)(^{35}Cl, ^{37}Cl)

EXAMPLE 39

1-(3-((S)-(4-Chlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl-(methylamino))butyl)-4-(2-(1'-(tetrazolyl)-methyl)-phenyl)-piperazine

1-t-Butoxycarbonyl-4-(2-((1', 2', 3', 4'-tetrazolyl)methyl)phenyl)-piperazine prepared in Example 33, Step C was subjected to the conditions described in Example 9 Step D, then reacted with 4-bromo-2-((S)-(4-Chlorophenyl))-4-((N-3,5-bis-trifluoromethylbenzoyl)methylamino)-butane (prepared in Example 30) according to the procedure described in Example 15 step C to give the title compound. MS(CI) 680(M^++H)

The compounds in Examples 40 to 44 were prepared by successively carrying out the procedures described in Example 9, Step D and Example 15, Step C, using the piperazines synthesized in Example 33, Step C for Example 40, Example 35, Step A for Examples 41 and 42, Example 37, Step A for Example 43, and Example 38, Step A for Example 44, which in each case are allowed to react with the bromide prepared in Example 30.

EXAMPLE 40

1-(3-((S)-(4-Chlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl-(methylamino))butyl)-4-(2-(2'-(tetrazolyl)methyl)phenyl)-piperazine

MS(CI) 680(M^++H)

EXAMPLE 41

1-(3-((S)-(4-Chlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl-(methylamino))butyl)-4-(2-(1'-(1', 2', 4'-triazolyl)methyl)phenyl)-piperazine

MS(CI) 679(M^++H)

EXAMPLE 42

1-(3-((S)-(4-Chlorophenyl))-4-(N-3,5-bis-trifluoromethylbenzoyl-(methylamino))butyl-4-(2-(4'-(1', 2', 4'-triazolyl)methyl)phenyl)-piperazine

MS(CI) 679(M^++H)

EXAMPLE 43

1-(3-((S)-(4-Chlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)-benzoyl(methylamino))butyl)-4-(2-(1'-(1', 2', 3'-triazolyl)-methyl)-phenyl)-piperazine

MS(CI) 679(M^++H)

EXAMPLE 44

1-(3-((S)-(4-Chlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl-(methylamino))butyl)-4-(2-(methanesulfonylaminomethyl)phenyl)-piperazine

MS(CI) 705(M^++H)

EXAMPLE 45

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-fluoro-5-(trifluoromethyl)-benzoyl(methylamino))butyl)-4-(2-(1'-(tetrazolyl)-methyl)phenyl)-piperazine

Step A: 3-((S)-(3,4-Dichlorophenyl))-4-((3-fluoro-5-dimethylbenzoyl)methyl-amino)-butanal

The title compound was prepared following the procedure described in Example 1, Step A using 3-fluoro-5-trifluoromethylbenzoic acid instead of 3,5-dimethylbenzoic acid.

Step B: 4-Bromo-2-((S)-(3,4-Dichlorophenyl))-4-((N-3-fluoro-5-trifluoromethylbenzoyl)methylamino)-butane

The aldehyde prepared in Step A was treated with the conditions described in Example 15, Steps A and B to give the title compound.

Step C: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-fluoro-5-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(1'-(tetrazolyl)-methyl)phenyl)-piperazine

1-t-Butoxycarbonyl-4-(2-(1'-(tetrazolyl)methyl)phenyl)-piperazine (prepared in Example 33, Step C) was deprotected according to the conditions in Example 9, Step D and the product was carried on according to Example 1, Step E using the aldehyde prepared in Step A above to give the title compound. MS(CI) 664(M^++H)(^{35}Clx2), 666(M^++H)(^{35}Cl, ^{37}Cl)

EXAMPLE 46

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-fluoro-5-(trifluoromethyl)-benzoyl(methylamino))butyl)-4-(2-(2'-(tetrazolyl)-methyl)phenyl)-piperazine

1-t-Butoxycarbonyl-4-(2-(2'-(tetrazolyl)methyl)phenyl)-piperazine (prepared in Example 33, Step C) was subjected to the conditions described in Example 45, Step C to give the title compound. MS(CI) 664(M^++H)(^{35}Clx2), 666(M^++H)(^{35}Cl, ^{37}Cl)

EXAMPLE 47

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-fluoro-5-trifluoromethyl-benzoyl(methylamino))butyl)-4-(2-(methanesulfonylaminomethyl)-phenyl)-piperazine

1-t-Butoxycarbonyl-4-(2-(methanesulfonylaminomethyl)phenyl)-piperazine prepared in Example 38, Step A was subjected to the conditions described in Example 45, Step C to give the title compound. MS(CI) 689(M^++H)(^{35}Clx2), 691(M^++H)(^{35}Cl, ^{37}Cl)

EXAMPLE 48

1-(3-((S)-(3,4-Dichlorophenyl))-4-((S)-(N-3,5-bis-(trifluoromethyl)-benzoyl(methylamino)))-5-hydroxy-pentyl)-4-(2-(1'-(tetrazolyl)-methyl)phenyl)-piperazine

Step A: Diazomethyl-(2-(S)-(3,4-dichlorophenyl)-pent-4-enyl)-ketone

To a solution of 2-(S)-(3,4-dichlorophenyl)-pent-4-enoic acid (5.04g, 20.6mmol) in 60mL of dichloromethane was added 2.15mL (24.6mmol) of oxalyl chloride and 0.1mL of dimethylformamide with cooling in an ice-water bath. The cooling bath was then removed and the reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure, and the resulting material was diluted in ethyl acetate and concentrated in vacuo in order to remove residual HCl. The residual crude acid chloride was dissolved in 70mL of ether and was slowly added to a 100mL ether solution of diazomethane (77mmol). After stirring for 2hr at rt, the solvent was removed under vacuum. The resulting yellow oil was chromatographed on silica gel column eluting with a gradient of hexane : ethyl acetate = 20 : 1 to 3 : 1 to give 4.66g (84%) of diazomethyl-(2-(S)-(3,4-dichlorophenyl)-pent-4-enyl)-ketone. ^{1}H-NMR ($CDCl_3$ 400MHz): δ 2.44(app. quint. 1H), 2.82(app. quint. 1H), 3.43(br s. 1H), 4.98 & 5.02 (d of AB quart., 2H), 5.16 (br s, 1H), 5.63(m, 1H), 7.09 (dd, J=2.2Hz, 8.3Hz, 1H), 7.34(d, J=2.2Hz, 1H), 7.38 (d, J=8.3Hz, 1H).

Step B: 3-(R)-(3,4-Dichlorophenyl)-hex-4-enoic acid

To a solution of the above diazoketone 4.56g (17.0mmol) in 340mL of tetrahydrofuran was added 170mL aquous solution of silver nitrate 3.02g (17.8mmol). After stirring at rt overnight, tetrahydrofuran was removed under reduced pressure. The remaining aqueous layer was extracted with two 100mL portions of dichloromethane. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The resulting material was purified by silica gel column chromatography. Elution with dichloromethane : methanol = 10 : 1 gave 3.94g (90%) of 3-(R)-(3,4-dichlorophenyl)-hex-4-eoic acid.

Step C: 3-(3(S)-(3,4-Dichlorophenyl)-2(S)-azido-1-oxo-5-hexenyl)-4(S)-benzyl-2-oxazolidinone

A solution of 3-(3(S)-(3,4-dichlorophenyl)-1-oxo-5-hexenyl)-4(S)-benzyl-2-oxazolidinone (190 mg, 0.45 mmol; prepared from 3-(R)-(3,4-dichlorophenyl)-hex-4-enoic acid (from Step B above) and 4(S)-benzyl-2-oxazolidinone according to the procedure of Evans, D. A.; et. al. *J. Am. Chem. Soc.* 1990, *112*, 4011-4030) in THF (2.5 mL) was added to a solution of KHMDS (1.0 mL of 0.5 M in $PhCH_3$, 0.50 mmol), and THF (1.5 mL) at -78°C. The reaction was maintained at -78°C for 30 min whereupon a solution of trisyl azide (177 mg, 0.57 mmol) and THF (1.5 mL) was added. The mixture was stirred for 2 min and HOAc (0.13 mL, 4.6 mmoL) was added. The reaction mixture was stirred 1 h in a 30°C water bath, whereupon it was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (silica gel 60, 15-25% EtOAc/hexanes) to afford the title compound (169 mg, 81%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.44 (d, 1H, J = 8.2 Hz), 7.20-7.46 (m, 6H), 7.15 (d, 1H, J = 8.3 Hz), 5.58-5.65 (m, 1H), 5.45 (d, 1H, J = 8.4 Hz), 5.03-5.05 (m, 1H), 4.97-5.02 (m, 1H), 4.64-4.70 (m, 1H), 4.26-4.34 (m, 2H), 3.28-3.36 (m, 2H), 2.88 (dd, 1H, J = 9.1, 13.5 Hz), 2.47 (t, 2H, J = 7.3 Hz) ppm.

Step D: 2(S)-Azido-3(S)-(3,4-dichlorophenyl)-5-hexen-1-ol

To a solution of 3-(3(S)-(3,4-dichlorophenyl)-2(S)-azido-1-oxo-5-hexenyl)-4(S)-benzyl-2-oxazolidinone (890 mg, 1.94 mmol) and THF (25 mL) at 0°C was added MeOH (126 mL, 3.1 mmoL), followed by $LiBH_4$ (68 mg, 3.1 mmol). The mixture was allowed to stir for 2 h, and was then quenched by addition of sat. aq. Rochelle salts (50 mL) and was allowed to warm to room temp and stirred vigorously for 2 h. The mixture was diluted with H_2O (150 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (silica gel 60, 10-40% EtOAc/hexanes) to afford the alcohol (452 mg, 82%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ

7.36-7.42 (m, 2H), 7.10 (dd, 1H, J = 2.1, 8.2 Hz), 5.59-5.69 (m, 1H), 5.09 (dd, 1H, J = 1.4, 17.1 Hz), 5.05 (dd, 1H, J = 0.9, 10.3 Hz), 3.77-3.85 (m, 1H), 3.65 (dd, 1H, J = 4.5, 11.2 Hz), 3.52 (dd, 1H, J = 7.6, 17.3 Hz), 2.88-2.95 (m, 1H), 2.55-2.64 (m, 1H), 2.43-2.52 (m, 1H), 1.28-1.34 (m, 1H) ppm. FTIR 3388, 2930, 2102, 1471, 1271, 1030, 930 cm^{-1}.

Step E: 2(S)-Amino-3(S)-(3,4-dichlorophenyl)-5-hexen-1-ol

A solution of 2(S)-azido-3(S)-(3,4-dichlorophenyl)-5-hexen-1-ol (620 mg, 2.17 mmol) and PPh_3 (682 mg, 2.60 mmol) in 4:1 THF/H_2O (20 mL)was stirred at room temp for 14 h and then heated to 65°C for 2 h. The reaction mixture was concentrated, and the residue diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (silica gel 60, 2.5-8% MeOH/CH_2Cl_2) to afford the amino alcohol (260 mg, 46%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40 (d, 1H, J = 8.3 Hz), 7.25-7.31 (m, 1H), 7.04 (dd, 1H, J = 1.9, 8.1 Hz), 5.51-5.61 (m, 1H), 4.92-5.03 (m, 2H), 3.68 (dd, 1H, J = 4.1, 10.7 Hz), 3.39 (dd, 1H, J = 7.4, 10.6 Hz), 3.01-3.08 (m, 1H), 2.68-2.75 (m, 1H), 2.49-2.56 (m, 1H), 2.32-2.41 (m, 1H) ppm.

Step F: 4(S)-(1(S)-(3,4-Dichlorophenyl)-3-butenyl)-2-oxazolidinone

A solution of 2(S)-amino-3(S)-(3,4-dichlorophenyl)-5-hexen-1-ol (3.85 g, 14.8 mmol) and triphosgene (4.39 g, 14.8 mmol) in THF (100 mL) was stirred at room temp for 2 h. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography (silica gel 60, 1-5% MeOH/CH_2Cl_2) to afford the oxazolidone (3.35 g, 79%) as a colorless solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.45 (d, 1H, J = 8.2 Hz), 7.25-7.31 (m, 1H), 7.05 (dd, 1H, J = 2.1, 8.3 Hz), 5.50-5.62 (m, 1H), 4.99-5.16 (m, 2H), 4.56 (t, 1H, J = 8.7 Hz), 4.21 (dd, 1H, J = 6.4, 9.0 Hz), 4.00-4.08 (m, 1H), 2.73-2.80 (m, 1H), 2.30-2.43 (m, 2H) ppm.

Step G: 4(S)-(1(S)-(3,4-Dichlorophenyl)-3-butenyl)-3-methyl-2-oxazolidinone

To a solution of 4(S)-(1(S)-(3,4-dichlorophenyl)-3-butenyl)-2-oxazolidinone (3.25 g, 11.4 mmol) in DMF (25 mL) at room temp was added NaH (573 mg, 95%, 22.7 mmol). The mixture was stirred for 20 min whereupon MeI (3.54 mL, 57.0 mmol) freshly filtered through basic alumina was added and the resultant reaction mixture was stirred at 70°C for 14 h. The cooled reaction mixture was diluted with H_2O (250 mL) and extracted with EtOAc (3 x 125 mL). The combined organic extracts were washed with H_2O (3 x 100 mL), brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (silica gel 60, 1-5% MeOH/CH_2Cl_2) to afford the title compound (2.93 g, 86%) as a colorless solid and recovered starting material (382 mg, 11%). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.45 (d, 1H, J = 8.3 Hz), 7.25-7.31 (m, 1H), 7.06 (dd, 1H, J = 2.1, 8.2 Hz), 5.52-5.62 (m, 1H), 4.99-5.08 (m, 2H), 4.12-4.26 (m, 2H), 3.82-3.90 (m, 1H), 3.00-3.07 (m, 1H), 2.75 (s, 3H), 2.38-2.49 (m, 2H) ppm. FTIR 2922, 1747, 1472, 1433, 1405, 1122, 1030, 914, 733 cm^{-1}.

Step H: 4(S)-(1(S)-(3,4-Dichlorophenyl)-3-oxopropyl)-3-methyl-2-oxazolidinone

The title compound was prepared from 4(S)-(1(S)-(3,4-dichlorophenyl)-3-butenyl)-3-methyl-2-oxazolidinone (prepared in Step G above) as in Example 1, Step A to afford the aldehyde (98%). ^1H NMR ($CDCl_3$, 500 MHz) δ 9.76 (s, 1H), 7.45 (d, 1H, J = 8.4 Hz), 7.25-7.31 (m, 1H), 7.06 (dd, 1H, J = 2.0, 8.5 Hz), 4.15-4.20 (m, 1H), 4.10 (dd, 1H, J = 5.5 Hz, 9.2 Hz), 3.88-3.94 (m, 1H), 3.72-3.78 (m, 1H), 2.99 (ddd, 1H, J = 0.9, 9.8, 17.8 Hz), 2.84 (s, 3H), 2.79 (dd, 1H, J = 4.1, 17.9 Hz) ppm.

Step I: 4(S)-(1(S)-(3,4-Dichlorophenyl)-3-(4-(2-(1'-(tetrazolyl)-methyl)phenyl)-1-piperazinyl)-propyl)-3-methyl-2-oxazolidinone

The title compound was prepared (77%) from 4(S)-(1(S)-(3,4-dichlorophenyl)-3-oxopropyl)-3-methyl-2-oxazolidinone (prepared in Step H above) and 1-(2-(1'-(tetrazolyl)-methyl)phenyl)-piperazine (prepared according to the procedure in Example 34) as in Example 1, Step E. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.52 (s, 1H), 7.47 (d, 1H, J = 8.3 Hz), 7.42 (dt, 1H,

J = 1.9, 8.1 Hz), 7.15-7.38 (m, 4H), 7.09 (dd, 1H, J = 2.1, 8.3 Hz), 5.66 (s, 2H), 4.26 (t, 1H, J = 8.9 Hz), 4.17 (dd, 1H, J = 6.2, 9.2 Hz), 3.82-3.90 (m, 1H), 3.07-3.14 (m, 1H), 2.80-2.92 (m, 4H), 2.73 (s, 3H), 2.50-2.61 (m, 2H), 2.38-2.50 (m, 2H), 2.20-2.33 (m, 2H), 1.65-1.90 (m, 3H) ppm.

Step J: 2(S)-Amino-3(S)-(3,4-dichlorophenyl)-5-(4-(2-(1'-(tetrazolyl))-methylphenyl)-1-piperazinyl))-pentan-1-ol

To a solution of 4(S)-(1(S)-(3,4-dichlorophenyl)-3-(4-(2-(1'-(tetrazolyl)-methyl)phenyl)-1-piperazinyl)-propyl)-3-methyl-2-oxazolidinone (88 mg, 0.166 mmol) and EtOH (2 mL) was added 1M aq KOH (2 mL). The resultant mixture was heated to 85°C for 14 h. The cooled mixture was then diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo yielding the amino alcohol (77 mg, 92%) as a colorless solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.52 (s, 1H), 7.08-7.42 (m, 7H), 5.66 (s, 2H), 3.76 (dd, 1H, J = 3.7, 11.2 Hz), 3.60 (dd, 1H, J = 3.9, 11.2 Hz), 2.80-2.96 (m, 4H), 2.63-2.68 (m, 1H), 2.52-2.62 (m, 2H), 2.40-2.51 (m, 2H), 2.31 (s, 3H), 2.14-2.22 (m, 3H), 2.04-2.14 (m, 2H) ppm.

Step K: 1-(3-((S)-(3,4-Dichlorophenyl))-4-((S)-(N-3,5-bis-(trifluoromethyl)benzoyl(methylamino)))-5-hydroxy-pentyl)-4-(2-(1'-(tetrazolyl)-methyl)phenyl)-piperazine

To a solution of 2(S)-amino-3(S)-(3,4-dichlorophenyl)-5-(4-(2-(1'-(tetrazolyl))-methylphenyl)-1-piperazinyl))-pentan-1-ol (24 mg, 0.048 mmol) and CH_2Cl_2 (1.5 mL) at 0°C was added Et_3N (13.3 mL, 0.096 mmol), and 3,5-bis(trifluoromethyl)benzoyl chloride (9.0 mL, 0.050 mmol). The resultant reaction mixture was stirred 30 min at 0°C whereupon it was purified directly, without concentration, by column chromatography (silica gel 60, 2.5-8 % MeOH/CH_2Cl_2) to afford the title compound (26 mg) as a colorless solid. Mass spectrum (CI): m/z = 744 (^{35}Cl + ^{35}Cl isotope + H^+), 746 (^{37}Cl + ^{35}Cl isotope + H^+).

EXAMPLE 49

1-(3-((S)-(3,4-Dichlorophenyl))-4-((S)-(N-3,5-bis-(trifluoromethyl)-benzoyl(methylamino)))-5-hydroxy-pentyl)-4-(2-(1'-(1',2',4'-triazolyl)-methyl)phenyl)-piperazine

Step A: 4(S)-(1(S)-(3,4-Dichlorophenyl)-3-(4-(2-(1'-(1',2',4'-triazolyl)-methyl)phenyl)-1-piperazinyl)-propyl)-3-methyl-2-oxazolidinone

The title compound was prepared (98%) from 4(S)-(1(S)-(3,4-dichlorophenyl)-3-oxopropyl)-3-methyl-2-oxazolidinone (prepared in Example 48, Step H) and 1-(2-(1'-(1',2',4'-triazolyl)-methyl)phenyl)-piperazine (prepared according to the procedure in Example 33, Step D) as in Example 1, Step E. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (s, 1H), 7.94 (s, 1H), 7.68 (dd, 1H, J = 7.1, 12.1 Hz), 7.45-7.60 (m, 2H), 7.32-7.40 (m, 2H), 7.09 (dd, 1H, J = 2.1, 8.2 Hz), 5.44 (s, 2H), 4.27 (t, 1H, J = 9.0 Hz), 4.17 (dd, 1H, J = 6.1, 9.1 Hz), 3.82-3.88 (m, 1H), 3.08-3.16 (m, 1H), 2.82-2.94 (m, 4H), 2.73 (s, 3H), 2.52-2.63 (m, 2H), 2.42-2.51 (m, 2H), 2.20-2.34 (m, 2H), 1.71-1.93 (m, 3H) ppm.

Step B: 2(S)-Amino-3(S)-(3,4-dichlorophenyl)-5-(4-(2-(1'-(1',2',4'-triazolyl))-methylphenyl)-1-piperazinyl))-pentan-1-ol

To a solution of 4(S)-(1(S)-(3,4-dichlorophenyl)-3-(4-(2-(1'-(tetrazolyl)-methyl)phenyl)-1-piperazinyl)-propyl)-3-methyl-2-oxazolidinone (78 mg, 0.147 mmol) and EtOH (2 mL) was added 1M aq KOH (2 mL). The resultant mixture was heated to 85°C for 14 h. The cooled mixture was then diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo yielding the amino alcohol (71 mg, 96%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (s, 1H), 7.95 (s, 1H), 7.06-7.72 (m, 7H), 5.44 (s, 2H), 3.77 (dd, 1H, J = 3.7, 11.5 Hz), 3.60 (dd, 1H, J = 3.9, 11.2 Hz), 2.80-2.96 (m, 4H), 2.61-2.67 (m, 1H), 2.53-2.61 (m, 2H), 2.42-2.52 (m, 2H), 2.32 (s, 3H), 2.16-2.27 (m, 3H), 2.07-2.15 (m, 2H) ppm.

Step C: 1-(3-((S)-(3,4-Dichlorophenyl))-4-((S)-(N-3,5-bis-(trifluoromethyl)benzoyl(methylamino)))-5-hydroxy-

pentyl)-4-(2-(1'-(1',2',4'-triazolyl)-methyl)phenyl)-piperazine

To a solution of 2(S)-amino-3(S)-(3,4-dichlorophenyl)-5-(4-(2-(1'-(1',2',4'-triazolyl))-methylphenyl)-1-piperazinyl))-pentan-1-ol (22 mg, 0.044 mmol) and CH_2Cl_2 (1.5 mL) at 0°C was added Et_3N (12.0 mL, 0.088 mmol), and 3,5-bis(trifluoromethyl)benzoyl chloride (8.3 mL, 0.046 mmol). The resultant reaction mixture was stirred 30 min at 0°C whereupon it was purified directly, without concentration, by column chromatography (silica gel 60, 2.5-8 % MeOH/CH_2Cl_2) to afford the title compound (20 mg) as a colorless solid. Mass spectrum (CI): m/z = 743 (^{35}Cl + ^{35}Cl isotope + H^+), 745 (^{37}Cl + ^{35}Cl isotope + H^+).

EXAMPLE 50

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine

Step A: 1-t-Butoxycarbonyl-4-(2-(methylthiomethyl)phenyl)-piperazine

Potassium t-butoxide (159 mg, 1,42 mmol) in 15 mL of abs. EtOH was saturated with methyl mercaptan gas. To this mixture was added 1-t-butoxycarbonyl-4-(2-(methanesulfonyloxymethyl)-phenyl)-piperazine (0.94 mmol, which was generated according to the procedure described in Step C of Example 9). The resulting mixture was refluxed for 50 min and concentrated. The residue was purified by preparative TLC (20% EtOAc in Hex) to give the title compound (157 mg). ^1H NMR (200 MHz, $CDCl_3$) δ 1.47 (s, 9H), 2.05 (s, 3H), 2.87 (t, 4H), 3.55 (t, 4H), 3.80 (s, 2H), 7.08 (m, 2H), 7.20 (dd, 1H), 7.35 (dd, 1H).

Step B: 1-(2-(Methylthiomethyl)phenyl)-piperazine

The title compound was prepared from 1-t-butoxy-carbonyl-4-(2-(methylthiomethyl)phenyl)-piperazine (from Step A above) according to the procedure given in Example 9, Step D, and was used below without further purification.

Step C: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine

The title compound was prepared from 1-(2-(methylthiomethyl)phenyl)-piperazine (from Step B above) and 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dimethylbenzoyl)methylamino)-butanal (see Example 1, Step A) according to the procedure given in Example 1, Step E. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.26 (s, 6H), 3.76 (s, 2H). Mass Spectrum (CI) m/z . 584, 586 (M^++1, M^++3).

EXAMPLE 51

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bistrifluoromethylbenzoyl)-(methylamino))-butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine

The title compound was prepared by analogy to the procedure given in Example 50, Step C, using 3-((S)-(3,4-dichlorophenyl))-4-((3,5-bis(trifluoromethyl)benzoyl)methylamino)-butanal (from Example 33, Step A) instead of 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dimethylbenzoyl)methylamino)-butanal. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H), 3.76 (s, 2H). Mass Spectrum (CI) m/z 692.1 (M^++1).

EXAMPLE 52

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-methylbenzoyl)-(methylamino))butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine

The title compound was prepared by analogy to the procedure given in Example 50, Step C, using 3-((S)-(3,4-dichlorophenyl))-4-((3-methylbenzoyl)methylamino)-butanal instead of 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dimethylbenzoyl)methylamino)-butanal. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.31 (s, 3H), 3.76 (s, 2H). Mass Spectrum (CI) m/z 570.3, 572.3 (M^++1, M^++3).

EXAMPLE 53

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine, S-oxide

The title compound was prepared from 1 equiv. of 1-(3-((S)-(3,4-dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine (from Example 50, Step C) and 1.5 equiv of oxone (potassium peroxymonosulfate) in MeOH/H_2O at 0°C for 6 min. ^1H NMR (400 MHz, $CDCl_3$) δ 2.27(s, 6H), 2.40 (s, 3H), 4.07 (d, 1H), 4.14 (d, 1H). Mass Spectrum (CI) m/z 600.2, 602.3 (M^++1, M^++3).

EXAMPLE 54

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bistrifluoromethylbenzoyl)-(methylamino))-butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine, S-oxide

The title compound was prepared according to the procedure given in Example 53, using 1-(3-((S)-(3,4-dichlorophenyl))-4-(N-3,5-bistrifluoromethylbenzoyl)-(methylamino))-butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine (from Example 51) as starting material. ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 4.06 (d, 1H), 4.15 (d, 1H). Mass Spectrum (CI) m/z 708.1 (M^++1).

EXAMPLE 55

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-methylbenzoyl)-(methylamino))butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine, S-oxide

The title compound was prepared according to the procedure given in Example 53, using 1-(3-((S)-(3,4-dichlorophenyl))-4-(N-3-methylbenzoyl)-(methylamino))butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine (from Example 52) as starting material. ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.40 (s, 3H), 4.07 (d, 1H), 4.13 (d, 1H). Mass Spectrum (CI) m/z 586.2, 588.2 (M^++1, M^++3).

EXAMPLE 56

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine, S, S-dioxide

The title compound was prepared from 1-(3-((S)-(3,4-dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine, S-oxide and 3 equiv of oxone in MeOH/H_2O at room temperature for 1 h. ^1H NMR (400 MHz, $CDCl_3$) δ 2.27(s, 6H), 2.67 (s, 3H), 4.39 (s, 2H). Mass Spectrum (CI) m/z 616.2 (M^++1).

EXAMPLE 57

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bistrifluoromethylbenzoyl)-(methylamino))-butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine, S, S-dioxide

The title compound was prepared from 1-(3-((S)-(3,4-dichlorophenyl))-4-(N-3,5-bistrifluoromethylbenzoyl)-(methylamino))-butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine, S-oxide and 3 equiv of oxone in MeOH/H_2O at room temperature for 1 h. ^1H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 6H), 4.39 (s, 2H). Mass Spectrum (CI) m/z 724.1 (M^++1).

EXAMPLE 58

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-methylbenzoyl)-(methylamino))-butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine, S, S-dioxide

The title compound was prepared from 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-methylbenzoyl)-(methylamino))butyl)-4-(2-(methylthiomethyl)phenyl)-piperazine, S-oxide and 3 equiv of oxone in MeOH/H_2O at room temperature for 1 h. ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.68 (s, 6H), 4.39 (s, 2H). Mass Spectrum (CI) m/z 602, 604.3 (M^++1, M^++3).

Additional compounds for Formula I can be prepared from the piperazine starting materials given in the following Examples 59 or Example 60 or from the sources listed below by using the methods given in Example 1, Step E, Example15, Step C or Example 17:

EXAMPLE 59

7-(1-Piperazinyl)triazolo(2,3-α)pyrimidine dihydrochloride

Step A: 7-(1-(4-t-Butyloxycarbonyl)piperazinyl)triazolo(2,3-α)pyrimidine

7-Chloro-triazolo(2,3-α)pyrimidine (*Chem. Pharm. Bull.*, **1959**, 7, 907)(1.01g, 6.54mmol), was suspended in isoamyl alcohol (25mL) and 1-(t-butyloxycarbonyl)piperazine (4.86g, 26.13mmol) was added. This solution (dissolution occurred readily upon warming) was heated under reflux, under nitrogen for 1hr and then the reaction mixture was cooled, evaporated to dryness and the residue was dissolved in CH_2Cl_2 (100mL) and 10% aqu. Na_2CO_3 (100mL). After shaking, the layers were separated and the organic layer was washed with 10% aqu. Na_2CO_3 (2 x 100mL) and the pooled organic layers were dried (over $MgSO_4$), filtered, and evaporated to dryness. This oily residue was dissolved in a little CH_2Cl_2, absorbed onto silica gel 60, and applied to a silica gel 60 column (3.5 x 22.0 cm), packed and developed in CH_2Cl_2. Fractions containing the required product were pooled and evaporated to dryness to give a white solid which was crystallized from CH_2Cl_2/Et_2O to give 1.47g of the title compound as a white crystalline solid. Yield 1.71g (5.63mmol, 86% yield) in two crops. Analysis calculated for $C_{14}H_{20}N_6O_2$ (304): C, 55.25; H, 6.62; N, 27.61, Found:C, 55.17; H, 6.32; N, 27.75.

Step B: 7-(1-Piperazinyl)triazolo(2,3-α)pyrimidine dihydrochloride

7-(1-(4-t-Butyloxycarbonyl)piperazinyl)triazolo(2,3-a)pyrimidine prepared as described in step A (0.301g, 0.99mmol), was dissolved in anhydrous HCO_2H (10mL) and allowed to stand at room temperature for $1\frac{1}{2}$hr and then was evaporated to dryness *in vacuo*. This residue was dissolved in a little H_2O and applied to a Dowex 1 x 2 (OH^- form) column (2 x 23cm). The column was developed with H_2O and fractions containing the required product were pooled and evaporated to dryness to give 0.21g. TLC indicated a small amount of starting

material remaining and the residue was then dissolved in CF_3CO_2H (10mL) and allowed to stand at room temperature for 45 min. The reaction was then evaporated to dryness slowly under a nitrogen stream and the residue was evaporated to dryness once from H_2O before being dissolved in a little H_2O and passed down a Dowex 1 x 2 (OH^-form) column (2 x 25cm) as before. Fractions containing the required product were pooled and evaporated to dryness to give the title compound as a white solid (0.21g, quantitative yield) in the free base form. Analysis calculated for $C_9H_{12}N_6 \cdot 1.7\ H_2O$ (234.86) C, 46.02; H, 6.61; N, 35.78, Found: C, 46.31; H, 6.01; N, 35.64.

A portion of this material (0.10g) was dissolved in EtOH (3.5mL) and 3.49M HCl in MeOH (1mL) was added. A white precipitate formed immediately which was removed by centrifugation after standing at room temperature for 4hr and was washed with cold EtOH (2 x 5mL) and Et_2O (5mL) to give 0.11g (0.407mmol) of the title compound as the dihydrochloride salt. Analysis calculated for $C_9H_{14}N_6Cl_2.0.7H_2O$ (289.75): C, 37.30; H, 5.36; N, 29.00, Found: C, 37.52; H, 5.17; N, 28.92.

EXAMPLE 60

7-(1-Piperazinyl)triazolo(2,3-α)pyrimidine dihydrochloride

Step A: 7-Chloro-triazolo(2,3-α)pyrimidine

This was prepared according to procedures given in *Chem. Pharm. Bull.*, 7, 907 (1959).

Step B: 7-(1-(4-t-Butyloxycarbonyl)piperazinyl)triazolo(2,3-α)pyrimidine

7-Chloro-triazolo(2,3-a)pyrimidine, prepared as described in Step A above (1.01 g, 6.54 mmol), was suspended in isoamyl alcohol (25 mL) and 1-(t-butyloxycarbonyl)piperazine (4.86 g, 26.13 mmol) was added. This solution (dissolution occurred readily upon warming) was heated under reflux, under nitrogen for 1 hr and then the reaction mixture was cooled, evaporated to dryness and the residue was dissolved in CH_2Cl_2 (100 mL) and 10% aq. Na_2CO_3 (100 mL). After shaking, the

layers were separated and the organic layer was washed with 10% aqu. Na_2CO_3 (2 x 100 mL) and the pooled organic layers were dried (over $MgSO_4$), filtered, and evaporated to dryness. This oily residue was dissolved in a little CH_2Cl_2, absorbed onto silica gel 60, and applied to a silica gel 60 column (3.5 x 22.0 cm), packed and developed in CH_2Cl_2. Fractions containing the required product were pooled and evaporated to dryness to give a white solid which was crystallized from CH_2Cl_2/Et_2O to give 1.47 g of the title compound as a white crystalline solid. Yield 1.71g (5.63 mmol, 86% yield) in two crops. Anal. Calc. for $C_{14}H_{20}N_6O_2$ (304): C, 55.25; H, 6.62; N, 27.61, Found: C, 55.17; H, 6.32; N, 27.75.

Step C: 7-(1-Piperazinyl)triazolo(2,3-α)pyrimidine dihydrochloride

7-(1-(4-t-Butyloxycarbonyl)piperazinyl)triazolo(2,3-a)pyrimidine , prepared as described in Step B above (0.301 g, 0.99 mmol), was dissolved in anhydrous HCO_2H (10 mL) and allowed to stand at room temperature for $1\frac{1}{2}$ hr and then was evaporated to dryness *in vacuo*. This residue was dissolved in a little H_2O and applied to a Dowex 1 x 2 (OH^- form) column (2 x 23 cm). The column was developed with H_2O and fractions containing the required product were pooled and evaporated to dryness to give 0.21 g. TLC indicated a small amount of starting material remaining and the residue was then dissolved in CF_3CO_2H (10 mL) and allowed to stand at room temperature for 45 min. The reaction was then evaporated to dryness slowly under a nitrogen stream and the residue was evaporated to dryness once from H_2O before being dissolved in a little H_2O and passed down a Dowex 1 x 2 (OH^- form) column (2 x 25 cm) as before. Fractions containing the required product were pooled and evaporated to dryness to give the title compound as a white solid (0.21 g, quantitative yield).in the free base form. Anal. Calc. for $C_9H_{12}N_6 \cdot 1.7H_2O$ (234.86): C, 46.02; H, 6.61; N, 35.78, Found: C, 46.31; H, 6.01; N, 35.64.

A portion of this material (0.10 g) was dissolved in EtOH (3.5 mL) and 3.49 M HCl in MeOH (1 mL) was added. A white precipitate formed immediately which was removed by centrifugation after standing at room temperature for 4 hr and was washed with cold EtOH (2 x 5 mL) and Et_2O (5 mL) to give 0.11 g (0.407 mmol) of the title

compound as the dihydrochloride salt. Anal. Calc. for $C_9H_{14}N_6Cl_2 \cdot 0.7H_2O$ (289.75): C, 37.30; H, 5.36; N, 29.00, Found: C, 37.52; H, 5.17; N, 28.92.

Additional starting materials may be prepared as described in US Patent 5,057,517:
6-(1-piperazinyl)-8-methylpurine dihydrochloride,
6-(1-piperazinyl)-8,9-dimethylpurine dihydrochloride,
6-(1-piperazinyl)-9-methyl-3-deazapurine dihydrochloride,
(i.e. 1-methyl-4-(1-piperazinyl)-1H-imidazo(4,5-c)pyridine dihydrochloride),
8-bromo-6-(1-piperazinyl)purine dihydrochloride,
8-bromo-9-methyl-6-(1-piperazinyl)purine dihydrochloride,
2,9-dimethyl-8-methylamino-6-(1-piperazinyl)purine dihydrochloride,
2,9-dimethyl-8-dimethylamino-6-(1-piperazinyl)purine dihydrochloride,
2,9-dimethyl-6-(1-piperazinyl)-8-(1-pyrrolidinyl)purine dihydrochloride,
8-methoxy-9-methyl-6-(1-piperazinyl)purine dihydrochloride,
9-methyl-6-(1-piperazinyl)-8-(1-pyrrolidinyl)purine dihydrochloride,
8-dimethylamino-9-methyl-6-(1-piperazinyl)purine dihydrochloride,
6-(1-piperazinyl)-2,8,9-trimethylpurine dihydrochloride,
2,8,-dimethyl-6-(1-piperazinyl)purine dihydrochloride,
2-chloro-9-methyl-6-(1-piperazinyl)purine dihydrochloride,
9-methyl-2-morpholino-6-(1-piperazinyl)purine dihydrochloride,
9-methyl-6-(1-piperazinyl)-2-(1-pyrrolidinyl)purine dihydrochloride,
9-methyl-2-methylamino-6-(1-piperazinyl)purine dihydrochloride,
2-dimethylamino-9-methyl-6-(1-piperazinyl)purine dihydrochloride,
2,8-bis(dimethylamino)-9-methyl-6-(1-piperazinyl)purine dihydrochloride,
2-methoxy-9-methyl-6-(1-piperazinyl)purine dihydrochloride,
9-methyl-6-(1-piperazinyl)-2-(2-propoxy)purine dihydrochloride,
2-dimethylamino-6-(1-piperazinyl)purine dihydrochloride,
2-amino-6-(1-piperazinyl)purine dihydrochloride,
2-methoxy-6-(1-piperazinyl)-9-(1-propyl)purine dihydrochloride,
2-methylthio-6-(1-piperazinyl)-9-(1-propyl)purine dihydrochloride,
2-ethoxy-9-methoxymethyl-6-(1-piperazinyl)purine maleate,

9-ethoxymethyl-2-methoxy-6-(1-piperazinyl)purine maleate,
9-cyclopropylmethyl-2-ethoxy-6-(1-piperazinyl)purine dihydrochloride,
2-methoxy-9-methoxyethyl-6-(1-piperazinyl)purine dihydrochloride,
2-methoxy-6-(1-piperazinyl)-9-(1-(2-propynyl)purine dihydrochloride,
9-(1-allenyl)-2-methoxy-6-(1-piperazinyl)purine dihydrochloride,
2-methoxy-6-(1-piperazinyl)-9-(1-(2-propenyl))purine dihydrochloride,
9-cyclopropyl-2-ethyl-6-(1-piperazinyl)purine,
2-ethyl-9-(1-(2,2,2-trifluoroethylamino))-6-(1-piperazinyl)purine,
2-ethyl-9-methyl-6-(1-piperazinyl)purine dihydrochloride,
2-methoxy-6-(1-piperazinyl)-9-(2-propyl)purine dihydrochloride,
2-methoxy-9-(1-(2-oxopropyl))-6-(1-piperazinyl)purine dihydrochloride,
9-(1-(2,2-difluoropropyl))-2-methoxy-6-(1-piperazinyl)purine,
2-ethyl-9-(2-fluoroethyl)-6-(1-piperazinyl)purine dihydrochloride,
2-methoxy-6-(1-piperazinyl)-9-(2-furanylmethyl)purine,
9-((1S,2R)-2-fluoro-1-methylpropyl)-2-methoxy-6-(1-piperazinyl)purine,
9-((1R,2S)-2-fluoro-1-methylpropyl)-2-methoxy-6-(1-piperazinyl)purine,
9-((1S,2S)-2-fluoro-1-methylpropyl)-2-methoxy-6-(1-piperazinyl)purine,
9-((1R,2R)-2-fluoro-1-methylpropyl)-2-methoxy-6-(1-piperazinyl)purine.

Additional starting materials may be prepared as described in US Patent 4,980,350:
4-methyl-2-(1-piperazinyl)pyrimidine dihydrochloride,
4,5-dimethyl-2-(1-piperazinyl)pyrimidine dihydrochloride,
4,6-dimethyl-2-(1-piperazinyl)pyrimidine dihydrochloride,
4,5,6-trimethyl-2-(1-piperazinyl)pyrimidine dihydrochloride,
6-(1-butyl)-4-methyl-2-(1-piperazinyl)pyrimidine dihydrochloride,
4-(2-butyl)-2-(1-piperazinyl)pyrimidine dihydrochloride,
4-methyl-5-methoxy-4-(1-piperazinyl)pyrimidine dihydrochloride,
2-methyl-4-(1-piperazinyl)-S-triazine dihydrochloride.

Additional starting materials may be prepared as described in US Patent No. 4,876,256:
6-methyl-2-(1-piperazinyl)pyridine dihydrochloride,
2-(1-piperazinyl)pyridine dihydrochloride.

Additional starting materials may be prepared as described in *J. Heterocyclic Chem.*, 27, 1559 (1990):

8,9-dihydro-1-methyl-5-(1-piperazinyl)-7*H*-thiopyrano(2,3-e)(1,2,4)triazolo(4,3-a)pyrimidine,

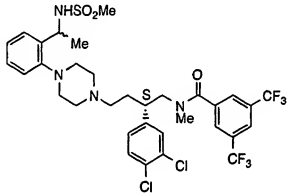
8,9-dihydro-5-(1-piperazinyl)-7*H*-thiopyrano(2,3-e)(1,2,4)triazolo(4,3-a)pyrimidine,

8,9-dihydro-5-(1-piperazinyl)-7*H*-tetrazolo(1,5-a)thiopyrano(2,3-e)pyrimidine,

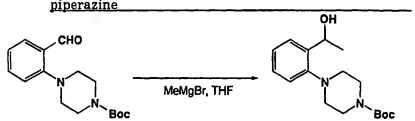
5,6-dihydro-7*H*-9-(1-piperazinyl)thiopyrano(3,2-d)(1,2,4)triazolo(2,3-a)pyrimidine.

EXAMPLE 61

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)-benzoyl(methylamino))butyl)-4-(2-(1-(R)-(methanesulfonyl-amino)ethyl)phenyl)-piperazine and 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl-(methylamino))butyl)-4-(2-(1-(S)-(methanesulfonylamino)ethyl]phenyl)-piperazine



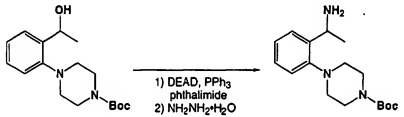
Step A: 1-t-butoxycarbonyl-4-(2-(1-(RS)-hydroxyethyl)phenyl)-piperazine



To a solution of 1g of 1-t-butoxycarbonyl-4-(2-formylphenyl)-piperazine (3.44mmol) (prepared as described in example 9 step A) in THF 30ml was added methylmagnesium bromide (3M THF solution) 1.26ml (3.78mmol) with cooling in an ice-water bath. The cooling bath was then removed and the reaction mixture was stirred at rt for 1hr. The reaction was quenched by the addition of saturated NH_4Cl solution. After removal of THF under reduced pressure, the reaction mixture was diluted with ethyl acetate and water. Organic phase was separated. The aqueous phase was extracted twice with ethyl acetate, and the combined

org. phases were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with a hexanes/ethyl acetate mixture to give 919mg (87%) of the desired alcohol. ^{1}H-NMR (500MHz, CDCl3): d1.51(s, 9H), 1.55(d, J=6.5Hz, 3H), 2.91-2.97(m, 4H), 3.4-3.8(br s, 4H), 5.1(br s, 1H), 5.8(br s, 1H). Mass spectrum (CI) m/z 307 (M^++1).

Step B 1-t-butoxycarbonyl-4-(2-(1-(RS)-aminoethyl)phenyl)-piperazine

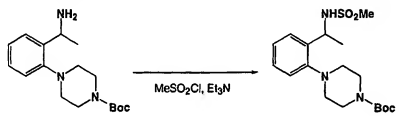


To a solution of 1g of the alcohol obtained in step A (3.26mmol) in THF 10ml was added 1.03g (3.93mmol) of triphenyphosphine and 624mg (4.24mmol) of phthalimide , and finally 0.565ml (3.44mmol) of diethylazodicarboxylate with cooling in an ice-water bath. The cooling bath was then removed and the reaction mixture was stirred at rt overnight. THF was removed under reduced pressure. The remaining material was diluted with ethyl acetate and water, and the organic phase was separated. The aqueous phase was extracted twice with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate, filtered, concentrated, and the residue was purified by flash chromatography on silica gel eluting with 10:1 to 3:1 hexanes/ethyl acetate to give 1.13g (79%) of the desired compound. ^{1}H-NMR (500HMz, CDCl3): d1.5 & 1.55 (s, 9H), 1.82(d, 3H), 2.7-2.82(br s, 4H), 3.2-4.0(br s, 4H), 6.1(m, 1H), 7.1-7.8(m, 8H).

To a solution of 1.13g (2.6mmol) of the compound obtained above dissolved in 25 mL of absolute ethanol was added 0.8ml (26mmol) of hydrazine hydrate and the reaction mixture was heated to reflux for 1.5hr. The voluminous precipitate of phthalimide was removed by filtration through a pad of celite. The filtrate was concentrated to give

750mg (95%) of the desired amine. This material was pure enough to be used in the next step. ^{1}H-NMR (500MHz, $CDCl_3$): d1.41(d, J=6.7Hz, 3H), 1.51(s, 9H), 2.85-2.87(br s, 4H), 4.6(q, J=6.7Hz, 1H), 7.1-7.5(m, 4H).

Step C: 1-t-butoxycarbonyl-4-(2-(1-(RS)-(methanesulfonyl-amino)ethyl)phenyl)-piperazine



This compound was synthesized following the procedure described in example 38 step A. ^{1}H-NMR (500MHz, $CDCl_3$): d1.51(s, 9H), 1.54(d, J=7Hz, 3H), 2.75(s, 3H), 2.8-3.0(br s, 4H), 3.3-3.9(br s, 4H), 5.05(m, 1H), 5.85(br s, 1H), 7.2-7.4(m, 4H). Mass spectrum (CI) m/z 284 (M^++1).

Step D: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(1-(R)-(methanesulfonylamino)ethyl)phenyl)-piperazine and 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(1-(S)-(methanesulfonylamino)ethyl)phenyl)-piperazine

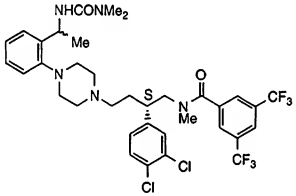
The title compounds were prepared as an inseparable mixture following the procedure described in example 33 step D. Mass spectrum: (CI) m/z 755(^{37}Cl+^{35}Cl), 753 (^{35}Clx2).

The compounds in example 62 -70 were prepared by reacting the requisite piperazine with either 3-((S)-3,4-dichlorophenyl))-4-((3,5-bistrifluoromethylbenzoyl)methylamino)butanal (Example 33 step A) or 3-((S)-3,4-dichlorophenyl))-4-((3-fluoro-5-trifluoromethylbenzoyl)-methylamino)butanal (Example 45 step A), or 3-((S)-4-chlorophenyl))-4-((3,5-bistrifluoromethylbenzoyl)methylamino)butanal (example 30) according to the procedure of Example 1, step E. The piperazine

substrates were synthesized by the method of example 61 step C by substituting the appropriate acylation agent. In each case diastereomeric mixtures were obtained.

EXAMPLE 62

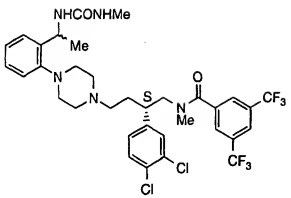
1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)-benzoyl(methylamino))butyl)-4-(2-(1-(R)-(dimethylamino-carbonylamino)ethyl)phenyl)-piperazine and 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl(methyl-amino))butyl)-4-(2-(1-(S)-(dimethylaminocarbonylamino)ethyl)phenyl)-piperazine



Mass spectrum: (CI) m/z 748 ($^{37}Cl+^{35}Cl$), 746($^{35}Clx2$).

EXAMPLE 63

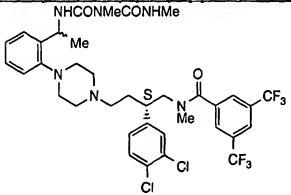
1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl-(methylamino))butyl)-4-(2-(1-(R)-(methylaminocarbonylamino)-ethyl)phenyl)-piperazine and 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(1-(S)-(methylaminocarbonylamino)ethyl)phenyl)-piperazine



Mass spectrum: (CI) m/z 734 ($^{37}Cl+^{35}Cl$), 732(^{35}Clx2).

EXAMPLE 64

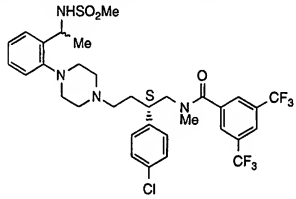
1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl-0(methylamino))butyl)-4-(2-(1-(R)-(methylaminocarbonyl(N-methyl)aminocarbonylamino)ethyl)phenyl)-piperazine and 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(1-(S)-(methylaminocarbonyl(N-methyl)aminocarbonylamino)ethyl)phenyl)-piperazine



Mass spectrum: (CI) m/z 791 ($^{37}Cl+^{35}Cl$), 789(^{35}Clx2).

EXAMPLE 65

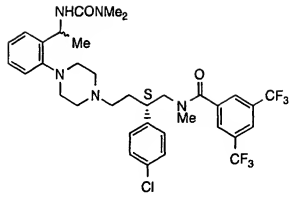
1-(3-((S)-(4-Chlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)-benzoyl(methylamino))butyl)-4-(2-(1-(R)-(methanesulfonylamino)-ethyl)phenyl)-piperazine and 1-(3-((S)-(4-Chlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(1-(S)-(methanesulfonylamino)ethyl)phenyl)-piperazine



Mass spectrum: (CI) m/z 721(^{37}Cl), 719(^{35}Cl).

EXAMPLE 66

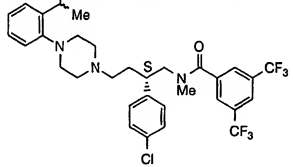
1-(3-((S)-(4-Chlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)-benzoyl(methylamino))butyl)-4-(2-(1-(R)-(dimethylaminocarbonyl-amino)ethyl)phenyl)-piperazine and 1-(3-((S)-(4-Chlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(1-(S)-(dimethylaminocarbonylamino)ethyl)phenyl)-piperazine



Mass spectrum: (CI) m/z 714(^{37}Cl), 712(^{35}Cl).

EXAMPLE 67

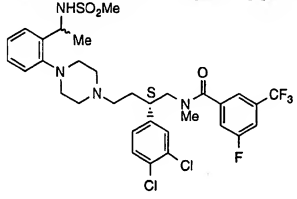
1-(3-((S)-(4-Chlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)-benzoyl(methylamino))butyl)-4-(2-(1-(R)-(methylaminocarbonyl-amino)ethyl)phenyl)-piperazine and 1-(3-((S)-(4-Chlorophenyl))-4-(N-3,5-bis-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(1-(S)-(methylaminocarbonylamino)ethyl)phenyl)-piperazine



Mass spectrum: (CI) m/z 701(^{37}Cl), 699(^{35}Cl).

EXAMPLE 68

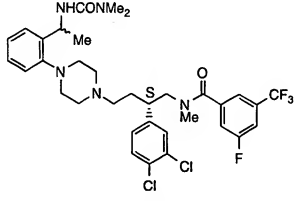
1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-fluoro-5-(trifluoromethyl)-benzoyl(methylamino))butyl)-4-(2-(1-(R)-(methanesulfonylamino)-ethyl)phenyl)-piperazine and 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-fluoro-5-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(1-(S)-(methanesulfonylamino)ethyl)phenyl)-piperazine



Mass spectrum: (CI) m/z 705($^{37}Cl+^{35}Cl$), 703($^{35}Clx2$).

EXAMPLE 69

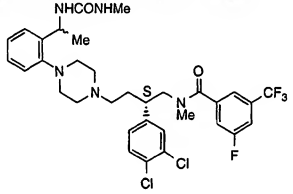
1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-fluoro-5-(trifluoromethyl)-benzoyl(methylamino))butyl)-4-(2-(1-(R)-(dimethylaminocarbonyl-amino)ethyl)phenyl)-piperazine and 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-fluoro-5-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(1-(S)-(dimethylaminocarbonylamino)ethyl)phenyl)-piperazine



Mass spectrum: (CI) m/z 698(^{37}Cl+^{35}Cl), 696(^{35}Clx2).

EXAMPLE 70

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-fluoro-5-(trifluoromethyl)-benzoyl(methylamino))butyl)-4-(2-(1-(R)-(methylaminocarbonyl-amino)ethyl)phenyl)-piperazine and 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-fluoro-5-(trifluoromethyl)benzoyl(methylamino))butyl)-4-(2-(1-(S)-(methylaminocarbonylamino)ethyl)phenyl)-piperazine



Mass spectrum: (CI) m/z 684(^{37}Cl+^{35}Cl), 682(^{35}Clx2).

EXAMPLE 71

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine

Step A: t-Butoxycarbonyl-4-(2-nitro)phenyl-piperazine

To a 30 ml DMF solution of t-butylpiperazine carboxylate 10g (53.7mmol) and o-fluoronitrobenzene 8.35g (59.2mmol) were added potassium carbonate 14.9 g (107.4 mmol). The reaction mixture was stirred at 150 °C in an oil bath overnight. After cooling to rt, the reaction mixture was concentrated under reduced pressure. The residual material was suspended in Et_2O and filtered through a pad of celite. The filtrate was washed with sat NH_4Cl aq. solution, dried over anhydrous Na_2SO_4, filtered, concentrated, and chromatographed

(silica, Hexanes : EtOAc = 10:1 to 7:1) to give 17.7g of the title compound. ^{1}H-NMR (500MHz $CDCl_3$) δ 1.49 (s, 9H), 3.02 (bs, 4H), 3.59 (bt, 4H, J = 4.8 Hz), 7.10 (t, 1H, J = 7.1 Hz), 7.15 (d, 1H, J = 7.1 Hz), 7.50 (t, 1H, J = 6.6 Hz), 7.79 (d, 1H, J = 8.2 Hz).

Step B: 1-t-Butoxycarbonyl-4-(2-amino)phenyl-piperazine

To a solution of 1-t-Butoxycarbonyl-4-(2-nitro)phenyl-piperazine (3.38g, 11 mmol) in 40 ml of methanol was added 0.2 g of (10% Pd on carbon). The reaction mixture was shaken under 50 psi of hydrogen for 18 h. The solution was then filtered through a plug of celite, concentrated, chromatographed on silica gel column eluting with Hexanes : EtOAc = 4:1 to give 2.61g (86%) of the title compound. ^{1}H-NMR (500MHz CDCl3) δ 1.51 (s, 9H), 2.87 (bs, 4H), 3.58 (bs, 4H), 4.00 (bs, 2H), 6.75-6.77 (m, 2H), 6.95-6.99 (m, 2H).

Step C: 4-(2-(Acetylamino)phenyl)-piperazine

A solution of 8.5 g (30.7 mmol) of 4-(2-amino)-phenyl-1-t-butoxycarbonylpiperazine (from Step B above) in 150 mL of CH_2Cl_2 was treated with 8.7 mL (90 mmol) of acetyl chloride and 7.5 mL (90 mmol) of pyridine. After stirring for 12 hr the reaction mixture was diluted with 200 ml CH_2Cl_2 and washed with water, saturated $NaHCO_3$, brine and dried over $MgSO_4$. After the filtrate was concentrated, the residue was dissolved in 150 ml of THF and to it was added 50 ml of concentrated HCl and the reaction was stirred at rt. After 30 min., the reaction mixture was diluted with 200 ml of water and it was washed with EtOAc. The aqueous fraction was brought to pH = 12 by careful addition of solid KOH and extracted with EtOAc. The organic fractions were washed with dilute NaOH and dried over $MgSO_4$. The filtrate was concentrated and chromatographed on a silica gel column eluting with $CHCl_3$: CH_3OH = 4:1 to furnish 4.2 g (63%) of the title compound. ^{1}H-NMR (500MHz $CDCl_3$) δ 2.22 (s, 3H, Ac), 2.86 (m, 4H, NCH_2), 3.08 (m, 4H, NCH_2), 6.76 - 7.18 (m, 4H, ar-H), 8.35 (d, 1H), 8.52 (br, 1H).

Step D: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-(2-(acetylaminomethyl)phenyl)-piperazine

To a solution of 0.895 g (2.57 mmol) of 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dichlorobenzoyl)methylamino)butanal (from Example 2, Step A) in 40 mL of dichloroethane were added 0.676 g (3.1 mmol) of 4-(2-acetylamino)phenyl-piperazine (Step C),and 0.818 g (3.85 mmol) of NaB(OAc)3H and the reaction mixture was stirred at rt. After 2 hr, the reaction was diluted with 100 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$, brine and dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was purified by HPLC (RCM SepPak, silica 25x100, 4.5% CH_3CN, 0.1% diisopropylamine in $tBuOCH_3$) to give 1.15 gm of the title compound. ^1H NMR (CD_3CN, ppm ranges are given because of amide rotamers and line broadening) δ 2.09 (s, 3H, Ac), 2.79 (s, 3H, NMe), 6.62-7.53 (m, 9H, ar-H), 8.16 (m, 1H, ar-H), 8.40 (br, 1H, N-H); Mass Spectrum (ESI): m/e 621, 623, 625, 627 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 72

1-(3-((R)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine

The title compound was prepared according to procedures described in Example 71. In this example (R)-(3,4-dichlorophenyl)-4-methylamino-1-pentene was employed in place of (S)-(3,4-dichlorophenyl)-4-methylamino-1-pentene (Example 71, Step A) to prepare the requisite 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dichlorobenzoyl) methylamino)butanal . ^1H NMR (CD_3CN, ppm ranges are given because of amide rotamers and line broadening) δ 2.09 (s, 3H, Ac), 2.79 (s, 3H, NMe), 6.62-7.53 (m, 9H, ar-H), 8.16 (m, 1H, ar-H), 8.40 (br, 1H, N-H); Mass Spectrum (ESI): m/e 621, 623, 625, 627 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 73

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-((2-nitro)phenyl)-piperazine

Step A: 4-(2-nitro)phenyl-piperazine

To a solution of 2.2 gm (7.16 mmol) of t-butoxycarbonyl-4-(2-nitro)phenyl-piperazine in 10 ml of CH_2Cl_2 was added 5 ml of trifluoroacetic acid and the reaction mixture was stirred for 2 hr. The reaction mixture was concentrated and the residue was redissolved in CH_2Cl_2, washed with brine and saturated $NaHCO_3$. The organic fractions were dried over Na_2SO_4, filtered and the filtrate was concentrated to give 1.16 gm of the title compound as a red oil. The material was used in Step B below without further purification.

Step B: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-(2-(nitro)phenyl)-piperazine

To a solution of 0.102 g (0.49 mmol) of 4-(2-nitro)phenyl-piperazine (Step A) in 1 ml of 1,2-dichloroethane were added 0.101 g (0.24 mmol)of 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dichlorobenzoyl)methyl-amino)butanal (from Example 2, Step A) in 4 mL of 1,2-dichloroethane. After stirring the mixture for 5 min, a solution of 0.103 g (0.49 mmol) of $NaCNBH_3$ was added. Some gas evolution was observed. After 3 h when the reaction was complete by TLC the mixture was filtered through a pad of celite, the reaction flask and the pad were rinsed with MeOH. The filtrate was concentrated to approximately 2 mL and the residue was diluted with Et_2O:EtOAc. The Et_2O:EtOAc solution was washed with water, brine and dried over Na_2SO_4. The filtrate was concentrated and the residue was purified by chromatography (silica, 1:2 acetone:hexanes) to isolate 0.148 g (100%) of the title compound as a white solid. ^1H NMR ($CDCl_3$, ppm ranges are given because of amide rotamers and line broadening). ^1H-NMR (500MHz $CDCl_3$) δ 1.60-3.83 (m, 18H), 6.81-7.44 (m, 8 H) , 7.48 (t, 1H, J = 8.0 Hz), 7.75 (d, 1H, J = 8.1 Hz). Mass Spectrum (CI)609, 611, 613, 615 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 74

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-amino)phenyl)-piperazine

A mixture of 0.195 gm (0.32 mmol) of 1-(3-((S)-(3,4-dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-(2-(nitro)phenyl)-piperazine and 0.296.6 gm (1.315 mmol) of $SnCl_2.2H_2O$ was placed under vacuum for 1.5h. To this mixture in a nitrogen atmosphere was added 3 ml of EtOH and the reaction mixture was heated at reflux for 90 min. The reaction mixture was diluted with 10 ml of EtOAc. The solution was washed with water, brine and dried over Na_2SO_4. The filtrate was refiltered through a pad of celite and concentrated to give the title compound as an oil. This material was used in the examples below without further purification. ^1H NMR ($CDCl_3$, ppm ranges are given because of amide rotamers and line broadening) δ 1.62-3.95 (20 H), 6.72-7.46 (m, 10 H).

EXAMPLE 75

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-formylamino)phenyl)-piperazine

To a solution of 0.133 gm (0.59 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and 0.159 gm of dimethylaminopyridine (DMAP) in 2 ml of CH_2Cl_2 at 0°C was added 0.0164 ml (0.43 mmol) of formic acid. After stirring for 5 min. the solution was added to a solution of 0.051 gm (0.088 mmol) of 1-(3-((S)-(3,4-dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-amino)phenyl)-piperazine in 2 ml of CH_2Cl_2 and the reaction mixture was stirred at rt for 4 hr. The reaction mixture was further diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered through a pad of silica and concentrated. The residue was purified by chromatography (silica, 1:3 acetone: hexanes) to give 0.017 gm of the title compound. ^1H NMR (500MHz $CDCl_3$) δ 1.61-3.87 (18H), 6.83-7.46 (m, 10H), 8.11-8.87 (m, 2H). Mass Spectrum (CI) 607, 609, 611, 613 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

The compounds in Examples 76 to 81 were prepared according to the procedure described in Example 75. The corresponding carboxylic acids are commercially available.

EXAMPLE 76

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-((2-n-butyrylamino)phenyl)-piperazine
Mass Spectrum (CI) 649, 651, 653 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 77

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-((2-n-propionylamino)phenyl)-piperazine
Mass Spectrum (CI) 635, 637, 639 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 78

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-((2-(3-methylbut-2-enoylamino)phenyl)-piperazine
Mass Spectrum (CI) 661, 663, 665 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 79

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-((2-methoxycarbonylamino)phenyl)-piperazine
The title compound was prepared according to procedures described in Example 75, but utilizing methylchloroformate. Mass Spectrum (CI) 637, 639, 641 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 80

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-((2-ethoxycarbonylamino)phenyl)-piperazine

The title compound was prepared according to procedures described in Example 75, but utilizing ethylchloroformate. Mass Spectrum (CI) 651, 653, 655 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 81

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-methansulfonylamino)phenyl)-piperazine

The title compound was prepared according to procedures described in Example 75, but utilizing methanesulfonyl chloride. Mass Spectrum (CI) 656, 658, 660 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern)

EXAMPLE 82

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-4-methoxybenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine

Step A: 3-((S)-(3,4-Dichlorophenyl))-4-((t-butoxycarbonyl) methylamino) -1-pentene

To a solution of 8.89 g (36.4 mmol) of 3-(S)-(3,4-dichlorophenyl)-4-methylamino-1-pentene (prepared as described by J. Hale *et al.*, *Bioorganic and Medicinal Chemistry Letters*, **1993**, *3*, 319-322) in 80 mL of CH_2Cl_2 was added 40 mL of 15% NaOH solution. With vigorous stirring, 11.9 gm of Boc_2O was slowly added over 30 min. After stirring for 30 min, the layers were separated and the organic layer was washed with saturated $NaHCO_3$ and brine. The solution was dried over Na_2SO_4 and concentrated to give 17 g of the title compound as an oil.

Step B: 3-((S)-(3,4-Dichlorophenyl))-4-((t-butoxycarbonyl) methyl-amino) -butanal

The title compound 1.96 gm) was prepared from 2 gm (5.81 mmol) of 3-((S)-(3,4-dichlorophenyl))-4-((t-butoxycarbonyl)methyl-amino) -1-pentene (Example 82, Step A) according to procedures described in Example 2, Step A. The reaction mixture was filtered through a thin pad of silica gel and the filtrate was concentrated. The residue was used in the next step without purification.

Step C: 1-(3-((S)-(3,4-Dichlorophenyl))-4-((N-t-butoxycarbonyl) methyl-amino)butyl)-4-((2-acetylamino)phenyl)-piperazine

The title compound (2.61 gm) was prepared from 2 gm (5.8 mmol) of 3-((S)-(3,4-dichlorophenyl))-4-((t-butoxycarbonyl) methyl-amino)-butanal (Example 82, Step B) and 1.53 gm (7 mmol) of 4-(2-(acetylamino)phenyl)-piperazine (Example 71, Step C) according to procedures described in Example 71, Step D). ^{1}H NMR (CD_3CN, ppm ranges are given because of amide rotamers and line broadening) δ 1.32 (s, 9H, O^{t}Bu), 2.10 (s, 3H, Ac), 2.69 (s, 3H, NMe), 7.03-7.10 (m, 2H, ar-H), 7.18-7.22 (m, 2H, ar-H), 7.44-7.48 (m, 2H, ar-H), 8.17 (m, 1H, ar-H), 8.41 (br, 1H, N-H); Mass Spectrum (ESI): m/e 549, 551, 553 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

Step D: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(methylamino)butyl)-4-((2-acetylamino)phenyl)-piperazine

To a solution of 0.85 gm (1.55 mmol) of 1-(3-((S)-(3,4-dichlorophenyl))-4-((N-t-butoxycarbonyl)methyl-amino)butyl)-4-((2-acetylamino)phenyl)-piperazine in 50 mL of EtOAc was added 50 mL of 70% HCl and the reaction was stirred 45 min at rt. The layers were separated and the aqueous fraction was brought to pH = 12 by careful addition of solid KOH and extracted with EtOAc. The organic fractions were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography (silica, CH3OH: CH_2Cl_2, 1:5) to give 0.76 gm of the title compound. ^{1}H NMR (CD_3CN, ppm ranges are given because of amide rotamers and line broadening) δ 2.12 (s, 3H, Ac), 2.71 (s, 3H, NMe), 7.03-7.10 (m, 2H, ar-H), 7.18-7.22 (m, 2H, ar-H), 6.64 - 7.58 (m, 6H, ar-H), 8.14 (m, 1H, ar-H), 8.41 (br, 1H, N-H); Mass Spectrum (ESI): m/e 449, 451, 453 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

Step E: 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-4-methoxybenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine

To a solution of 0.1 gm (0.22 mmol) of 1-(3-((S)-(3,4-dichlorophenyl))-4-(methylamino)butyl)-4-((2-acetylamino)phenyl)-piperazine in 2.5 mL of CH_2Cl_2 was added 0.05 mL (0.62 mmol) of

pyridine and 0.076 gm (0.44 mmol) of p-anisoylchloride and the reaction mixture was stirred at rt. After 24 hr, 50 mL of EtOAc was added and the solution was washed with saturated $NaHCO_3$ and brine. The organic fraction was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography (silica, 2% CH_3OH in CH_2Cl_2) to give 0.096 gm of the title compound. ^1H NMR ($CHCl_3$, ppm ranges are given because of amide rotamers and line broadening) δ 2.20 (s, 3H, Ac), 2.89 (s, 3H, NMe), 3.84 (s, 3H, OMe), 6.69-7.53 (m, 10H, ar-H), 8.34 (m, 1H, ar-H), 8.43 (br, 1H, N-H); Mass Spectrum (ESI): m/e 583, 585, 587 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

The compounds in Examples 83-111 were prepared by reacting 1-(3-((S)-(3,4-dichlorophenyl))-4-methyl-amino)butyl)-4-((2-acetylamino)phenyl)-piperazine with the requisite acid chlorides as dsecribed in Example 79.

EXAMPLE 83

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,4-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 621, 623, 625, 627 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 84

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-benzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 553, 555, 557 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).EXAMPLE 85

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-4-chlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 587, 589, 591, 593 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 86

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-chlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 587, 589, 591, 593 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 87

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-2-chlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine

Mass Spectrum (ESI): m/e 587, 589, 591, 593 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 88

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-4-methylbenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 567, 569, 571 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 89

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-4-ethylbenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 581, 583, 585 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 90

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-trifluoromethylbenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 621, 623, 625 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 91

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-4-i-propyloxybenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine

Mass Spectrum (ESI): m/e 611, 613, 615 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 92

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-methyl-4-chlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 601, 603, 605 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 93

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethoxybenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 613, 615, 617 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 94

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-2,6-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 601, 603, 605, 607 (M^+-19 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 95

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-trifluoromethyl-4-fluorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 639, 641, 643 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 96

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-2,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 621, 623, 625, 627 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).EXAMPLE 97

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-2,3-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine

Mass Spectrum (ESI): m/e 621, 623, 625, 627 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).EXAMPLE 98

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-2-trifluoromethylbenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine

Mass Spectrum (ESI): m/e 621, 623, 625 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).EXAMPLE 99

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-naphth-1-oyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine

Mass Spectrum (ESI): m/e 603, 605, 609 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 100

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-naphth-2-oyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine

Mass Spectrum (ESI): m/e 603, 605, 609 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 101

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-4-trifluoromethylbenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine

Mass Spectrum (ESI): m/e 621, 623, 625 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 102

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-2-methoxybenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine

Mass Spectrum (ESI): m/e 583, 585, 587 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 103

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-fluorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 571, 573, 575 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 104

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-trifluoromethylbenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 689 (M^++1).

EXAMPLE 105

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-cyanobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 578 (M^++1).

EXAMPLE 106

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-nitrobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 598, 590, 592 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 107

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethyl-4-fluorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 599, 601, 603 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 108

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-iodobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine
Mass Spectrum (ESI): m/e 679, 681, 683 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 109

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dibromobenzoyl)-(methylamino))butyl)-4-((2-acetylamino)phenyl)-piperazine

Mass Spectrum (ESI): m/e 709, 711, 713, 715 (M^++1 / $^{35}Cl/^{37}Cl$-$^{79}Br/^{81}Br$-isotope pattern).

EXAMPLE 110

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methylamino))butyl)-4-((2-acetylamino)phenyl)-piperazine

Mass Spectrum (ESI): m/e 581, 583, 585 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 111

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-acetyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine

Mass Spectrum (ESI): m/e 491, 493, 495 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

The compounds in Examples 112-120 were prepared by reacting the requisite piperazine with 3-((S)-(3,4-dichlorophenyl))-4-((3,5-dichlorobenzoyl)methylamino) butanal (from Example 2, Step A) according to the procedure of Example 71, Step D. The piperazine substrates were purchased or synthesized by the indicated procedures.

EXAMPLE 112

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-(4-trifluoromethylphenyl)-piperazine

Mass Spectrum (CI) 632, 634, 636(M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 113

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-(4-acetylphenyl)-piperazine

Mass Spectrum (CI) 606, 608, 610 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 114

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-(4-methylphenyl)-piperazine

Mass Spectrum (CI) 578, 580, 582 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 115

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-(4-chlorophenyl)-piperazine

Mass Spectrum (CI) 598, 600, 602 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 116

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-(4-fluorophenyl)-piperazine

Mass Spectrum (CI) 582, 584, 586 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 117

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-(4-nitrophenyl)-piperazine

Mass Spectrum (CI) 609, 611, 613 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 118

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-(3-trifluoromethylphenyl)-piperazine

Mass Spectrum (CI) 632, 634, 636 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 119

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-(3-methylphenyl)-piperazine

Mass Spectrum (CI) 578, 580, 582 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 120

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-(2-cyanophenyl)-piperazine

Mass Spectrum (CI) 588, 590, 592 (M^++1 / $^{35}Cl/^{37}Cl$-isotope pattern).

EXAMPLE 121

1-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-phenylpiperazine

A mixture of 3-((S)-(3-chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butanal (16 mg, 0.045 mmol) (prepared according to the procedure of Hale, J.J.; Finke, P.E.; MacCoss, M. *Bioorganic & Medicinal Chemistry Letters* **1993**,*3*, 319-322 and Example 1 except using phenylsulfonyl chloride in place of the benzoyl chloride in the acylation), 1-phenylpiperazine (22 mg, 0.136 mmol), 4A molecular sieves (25 mg) and acetic acid (0.008 mL, 0.136 mmol) in THF (1 mL) was stirred at rt for 20 min. Sodium triacetoxyborohydride (19 mg, 0.090 mmol) was then added and the reaction was stirred at rt for 16 h. The mixture was poured into a water containing excess sodium carbonate and was extracted twice with ethyl acetate. The organic layers were washed with brine, dried, combined and concentrated in vacuo. The residue was purified by prep TLC using 2% triethylamine in 85% ethyl acetate/hexanes as eluent to afforded the title compound (17 mg). Mass Spectrum (ESI) M+H = 498, 450

Using essentially the same procedure as Example 121 but employing the corresponding substituted piperazine, the following Examples were prepared.

EXAMPLE 122

1-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-(2-methylphenyl)piperazine

Mass Spectrum (ESI) M+H = 512, 514

EXAMPLE 123

1-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-(3-hydroxyquinoxalin-2-yl)piperazine

Mass Spectrum (NH_3/CI) M+H = 566, 568

EXAMPLE 124

1-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-(4-pyridyl)piperazine

Mass Spectrum (NH_3/CI) M+H = 499, 501

EXAMPLE 125

1-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-benzylpiperazine

Mass Spectrum (NH_3/CI) M+H = 512, 514

EXAMPLE 126

1-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-(2-methoxyphenyl)piperazine

Mass Spectrum (NH_3/CI) M+H = 528, 530

EXAMPLE 127

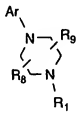
1-(3-((R,S)-Phenyl)-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-(pyrimidin-2-yl)piperazine

Mass Spectrum (NH_3/CI) M+H = 466

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A method for modulation of chemokine receptor activity in a mammal comprising the administration of an effective amount of a compound of formula I:



I

wherein the nitrogen attached to R_1 shown above is optionally quaternized with C_{1-4}alkyl or phenylC_{1-4}alkyl or is optionally present as the N-oxide (N+O-), and wherein:

R_1 is selected from a group consisting of:

linear or branched C_{1-8} alkyl, linear or branched C_{2-8} alkenyl, wherein the C_{1-8} alkyl or C_{2-8} alkenyl is optionally mono, di, tri or tetra substituted, the substituents independently selected from:

(a) hydroxy,
(b) oxo,
(c) cyano,
(d) halogen which is defined to include Br, Cl, I, and F,
(e) trifluoromethyl,
(f) phenyl or mono, di or tri-substituted phenyl, the substituents independently selected from
  (1') phenyl,
  (2') hydroxy,
  (3') C_{1-3}alkyl,
  (4') cyano,
  (5') halogen,

(6') trifluoromethyl,
(7') -NR_6COR_7,
(8') -$NR_6CO_2R_7$,
(9') -NR_6CONHR_7,
(10') -$NR_6S(O)_jR_7$, wherein j is 1 or 2,
(11') -$CONR_6R_7$,
(12') -COR_6,
(13') -CO_2R_6,
(14') -OR_6,
(15') -$S(O)_kR_6$, wherein k is 0, 1 or 2,

(g) -NR_6R_7,
(h) -NR_6COR_7,
(i) -$NR_6CO_2R_7$,
(j) -NR_6CONHR_7,
(k) -$NR_6S(O)_j$-R_7,
(l) -$CONR_6R_7$,
(m) -COR_6,
(n) -CO_2R_6,
(o) -OR_6,
(p) -$S(O)_kR_6$,
(q) -NR_6CO-heteroaryl,
(r) -$NR_6S(O)_j$-heteroaryl, and
(s) heteroaryl, wherein heteroaryl is selected from the group consisting of:
(1') benzimidazolyl,
(2') benzofuranyl,
(3') benzoxazolyl,
(4') furanyl,
(5') imidazolyl,
(6') indolyl,
(7') isooxazolyl,
(8') isothiazolyl,
(9') oxadiazolyl,
(10') oxazolyl,
(11') pyrazinyl,

(12') pyrazolyl,
(13') pyridyl,
(14') pyrimidyl,
(15') pyrrolyl,
(16') quinolyl,
(17') tetrazolyl,
(18') thiadiazolyl,
(19') thiazolyl,
(20') thienyl, and
(21') triazolyl,

wherein the heteroaryl is unsubstituted or mono di or tri-substituted, the substituents independently selected from:

(a") phenyl,
(b") hydroxy,
(c") oxo,
(d") cyano,
(e") halogen, and
(f") trifluoromethyl;

Ar is selected from the group consisting of:

(1) phenyl,
(2) pyridyl,
(3) pyrimidyl,
(4) naphthyl,
(5) furyl,
(6) pyrryl,
(7) thienyl,
(8) isothiazolyl,
(9) imidazolyl,
(10) benzimidazolyl,
(11) tetrazolyl,
(12) pyrazinyl,
(13) quinolyl,
(14) isoquinolyl,

(15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,
(20) isoindolyl,
(21) purinyl,
(22) isoxazolyl,
(23) thiazolyl,
(24) oxazolyl,
(25) triazinyl, and
(26) benzthiazolyl,
(27) benzoxazolyl,
(28) imidazopyrazinyl,
(29) triazolopyrazinyl,
(30) naphthyridinyl,
(31) furopyridinyl,
(32) thiopyranopyrimidyl and the 5-oxide and 5-dioxide thereof,
(33) pyridazinyl,
(34) quinazolinyl,
(35) pteridinyl,
(36) triazolopyrimidyl,
(37) triazolopyrazinyl,
(38) thiapurinyl,
(39) oxapurinyl, and
(40) deazapurinyl,

wherein Ar items (1) to (40) are optionally mono or di-substituted, said substituents being independently selected from:

(a) C_{1-3} alkyl, unsubstituted or substituted with
(1') oxo,
(2') hydroxy,
(3') OR_6,
(4') halogen,
(5') trifluoromethyl,

(6') phenyl or mono, di or tri-substituted phenyl, the substituents independently selected from hydroxy, cyano, halogen, and trifluoromethyl,

(b) -$(CH_2)_nS(O)_k$-(C_{1-6} alkyl), wherein n is 0, 1 or 2,

(c) -$(CH_2)_nS(O)_j$-NH_2,

(d) -$(CH_2)_nS(O)_j$-NH(C_{1-6} alkyl),

(e) -$(CH_2)_nS(O)_j$-NHR_6,

(f) -$(CH_2)_nS(O)_j$-NR_6-(C_{1-6} alkyl),

(g) -$(CH_2)_nCONH_2$,

(h) -$(CH_2)_nCONH$-(C_{1-6} alkyl),

(i) -$(CH_2)_nCONHR_6$,

(j) -$(CH_2)_nCONR_6$-(C_{1-6} alkyl),

(k) -$(CH_2)_nCO_2H$,

(l) -$(CH_2)_nCO_2$-(C_{1-6} alkyl),

(m) -$(CH_2)_nNR_6R_7$,

(n) -$(CH_2)_nNH$-C(O)-C_{1-6}alkyl,

(o) -$(CH_2)_nNH$-C(O)NH_2,

(p) -$(CH_2)_nNH$-C(O)NHC_{1-6}alkyl,

(q) -$(CH_2)_nNH$-C(O)N-(diC_{1-6} alkyl),

(r) -$(CH_2)_nNH$-S(O)k-C_{1-6}alkyl,

(s) -$(CH_2)_nN(C_{1-3}$alkyl)-C(O)-N(diC_{1-6} alkyl),

(t) -$(CH_2)_n$-heteroaryl, -C(O)-heteroaryl or -$(CH_2)_n$-O-heteroaryl , wherein the heteroaryl is selected from the group consisting of:

(1') benzimidazolyl,

(2') benzofuranyl,

(3') benzoxazolyl,

(4') furanyl,

(5') imidazolyl,

(6') indolyl,

(7') isooxazolyl,

(8') isothiazolyl,

(9') oxadiazolyl,

(10') oxazolyl,

(11') pyrazinyl,

(12') pyrazolyl,
(13') pyridyl or oxopyridyl,
(14') pyrimidyl,
(15') pyrrolyl,
(16') quinolyl,
(17') tetrazolyl,
(18') thiadiazolyl,
(19') thiazolyl,
(20') thienyl, and
(21') triazolyl,

wherein the heteroaryl group of items (1') to (21') is unsubstituted, mono, di or tri substituted, the substituents selected from:

(a') hydrogen,
(b') C_{1-6} alkyl, branched or unbranched, unsubstituted or mono or di-substituted, the substituents being selected from hydrogen and hydroxy,
(c') hydroxy,
(d') oxo,
(e') -OR_6,
(f') halogen,
(g') trifluoromethyl,
(h') nitro,
(i') cyano,
(j') -NHR_6,
(k') -NR_6R_7,
(l') -$NHCOR_6$,
(m') -NR_6COR_7,
(n') -$NHCO_2R_6$,
(o') -$NR_6CO_2R_7$,
(p') -$NHS(O)_jR_6$,
(q') -$NR_6S(O)_jR_7$,
(r') -$CONR_6R_7$,
(s') -COR_6,

(t') $-CO_2R_6$, and
(u') $-S(O)_jR_6$;

R_6 is selected from:

(1) hydrogen,
(2) C_{1-6} alkyl, or mono or di-substituted C_{1-6} alkyl, the substituents independently selected from:
  (a) phenyl,
  (b) hydroxy,
  (c) oxo,
  (d) cyano,
  (e) halogen,
  (f) trifluoromethyl, and
(3) phenyl or mono di or tri-substituted phenyl, the substituents independently selected from:
  (a) hydroxy,
  (b) C_{1-3}alkyl,
  (c) cyano,
  (d) halogen,
  (e) trifluoromethyl;

R_7 is selected from:

(1) hydrogen,
(2) C_{1-6} alkyl, or mono or di-substituted C_{1-6} alkyl, the substituents independently selected from:
  (a) phenyl unsubstituted or substituted with
    (1') hydroxy,
    (2') C_{1-3}alkyl,
    (3') cyano,
    (4') halogen,
    (5') trifluoromethyl,
    (6') C_{1-3}alkyloxy,
  (b) hydroxy,
  (c) oxo,

(d) cyano,
(e) halogen,
(f) trifluoromethyl,

(3) phenyl or mono di or tri-substituted phenyl, the substituents independently selected from:
(a) hydroxy,
(b) C_{1-3}alkyl,
(c) cyano,
(d) halogen,
(e) trifluoromethyl,

(4) naphthyl or mono di or tri-substituted naphthyl, the substituents independently selected from:
(a) hydroxy,
(b) C_{1-3}alkyl,
(c) cyano,
(d) halogen,
(e) trifluoromethyl,

(5) C_{1-3}alkyloxy;

or R_6 and R_7 are joined together to form a 5-, 6-, or 7-membered monocyclic saturated ring containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and in which the ring is unsubstituted or mono or di-substituted, the substituents independently selected from:

(1) hydroxy,
(2) oxo,
(3) cyano,
(4) halogen,
(5) trifluoromethyl,

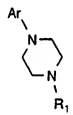
R_8 and R_9 are each independently hydrogen or substituted C_{1-4}alkyl wherein the substitutent is selected from the group consisting of

(1) hydroxy,
(2) hydrogen,

(3) cyano,
(4) halogen,
(5) trifluoromethyl,
(6) C_{1-3}alkyloxy,

provided that when Ar is phenyl, pyridyl or pyrimidyl, then Ar is mono di or tri-substituted;
and further provided that when Ar is mono substituted phenyl, then the substituent is other than halo, hydroxy, -OC_{1-4}alkyl, CF_3 or C_{1-4}alkyl;
and further provided that when Ar is di- or tri-substituted, at least one of the substituents is other than halo, hydroxy, -OC_{1-4}alkyl, CF_3 or C_{1-4}alkyl;
and pharmaceutically acceptable salts thereof.

2. The method of Claim 1 wherein the compound is of Formula Ia:



Ia

wherein:
R_1 is selected from a group consisting of:
C_3, C_4, C_5, C_6, C_7, C_8 linear or branched alkyl, unsubstituted or mono, di or tri-substituted, the substituents independently selected from:
(a) hydroxy,
(b) Cl or F,
(c) phenyl or mono, di or tri-substituted phenyl, the substituents independently selected from:
(1') phenyl,

(2') hydroxy,
(3') C_{1-3}alkyl,
(4') cyano,
(5') halogen,
(6') trifluoromethyl,

(d) -NR_6CO-R_7, wherein R_6 is hydrogen or C_{1-3} alkyl and R_7 is phenyl optionally substituted with Cl, F, CF_3 or C_{1-3}alkyl,

(e) -COR_6,

(f) -OR_6,

(g) -$NR_6S(O)j$-R_7, where j is 1 or 2,

(h) -$NR_6S(O)j$-heteroaryl, wherein heteroaryl is selected from the group consisting of:

(1') benzimidazolyl,
(2') benzofuranyl,
(3') benzoxazolyl,
(4') furanyl,
(5') imidazolyl,
(6') indolyl,
(7') isooxazolyl,
(8') isothiazolyl,
(9') oxadiazolyl,
(10') oxazolyl,
(11') pyrazinyl,
(12') pyrazolyl,
(13') pyridyl,
(14') pyrimidyl,
(15') pyrrolyl,
(16') quinolyl,
(17') tetrazolyl,
(18') thiadiazolyl,
(19') thiazolyl,
(20') thienyl, and
(21') triazolyl,

wherein the heteroaryl is unsubstituted or mono di or

tri-substituted, the substituents independently selected from:

(a') phenyl,
(b') hydroxy,
(c') oxo,
(d') cyano,
(e') halogen, and
(f') trifluoromethyl;

Ar is selected from the group consisting of:

(1) phenyl,
(2) pyrazinyl,
(3) pyrazolyl,
(4) pyridyl,
(5) pyrimidyl, and
(6) thienyl,

wherein the Ar is unsubstituted or mono or di-substituted, and substituents are independently selected from:

(a) C_{1-3} alkyl, unsubstituted or substituted with
(1') oxo,
(2') hydroxy,
(3') OR_6,
(4') halogen, and
(5') trifluoromethyl,
(b) $CONR_6$-(C_{1-2} alkyl),
(c) CO_2H,
(d) CO_2-(C_{1-2} alkyl),
(e) CH_2NR_6-(C_{1-2} alkyl),
(f) CH_2NH-C(O)-C_{1-3}alkyl,
(h) CH_2NH-C(O)NH_2,
(i) CH_2NH-C(O)NHC_{1-3}alkyl,
(j) CH_2NH-C(O)N-diC_{1-3} alkyl),
(k) CH_2NH-S(O)j-C_{1-3}alkyl,
(l) CH_2-heteroaryl, with the heteroaryl is selected from the group consisting of:

(1') imidazolyl,
(2') oxazolyl,
(3') pyridyl,
(4') tetrazolyl,
(5') triazolyl,
and the heteroaryl is unsubstituted, mono, di or tri-substituted, where the substituents selected from:
(a') hydrogen,
(b') C_{1-6} alkyl, branched or unbranched, unsubstituted or mono or di-substituted, the substituents being selected from hydrogen and hydroxy;

and pharmaceutically acceptable salts thereof.

3. The method of Claim 1 wherein the compound R_1 is selected from a group consisting of:
C_4, C_5, C_6, C_7 or C_8 linear or branched alkyl, which is mono, di- or tri-substituted, where the substituents are independently selected from:
(a) hydroxy,
(b) Cl or F,
(c) phenyl or mono or di-substituted phenyl, where the substituents are independently selected from:
(1') hydroxy,
(2') methyl or ethyl,
(3') Cl or F,
(4') trifluoromethyl,
(d) $-NR_6COR_7$, wherein R_6 is methyl and R_7 is phenyl optionally substituted with halo, CF_3, C_{1-3}alkyl or C_{1-3}alkoxy, and
(e) $-NR_6S(O)j-R_7$, where j is 1 or 2;

and pharmaceutically acceptable salts thereof.

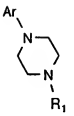
4. The method of Claim 1 wherein the compound Ar is mono substituted or di-substituted phenyl,

wherein the substituents are selected from the group consisting of:

(a) C_{1-3} alkyl, unsubstituted or substituted with
  (1') oxo,
  (2') hydroxy, or
  (3') OR_6, wherein R_6 is hydrogen or C_{1-3} alkyl,
(b) $-CH_2NR_6-(C_{1-2}$ alkyl),
(c) $-CH_2NH-C(O)-C_{1-3}$alkyl,
(d) $-CH_2NH-C(O)NH_2$,
(i) $-CH_2NH-C(O)NHC_{1-3}$alkyl,
(j) $-CH_2NH-C(O)N-diC_{1-3}$ alkyl),
(k) $-CH_2NH-S(O)j-C_{1-3}$alkyl,
(l) $-CH_2$-heteroaryl, where heteroaryl is selected from the group consisting of:
  (1') imidazolyl,
  (2') oxazolyl,
  (3') pyridyl,
  (4') tetrazolyl,
  (5') triazolyl,
  and where heteroaryl is unsubstituted, mono, di or tri substituted, where the substituents are independently selected from:
    (a') hydrogen,
    (b') C_{1-6} alkyl, branched or unbranched, unsubstituted or mono or disubstituted, where the substituents are selected from: hydrogen and hydroxy;

and pharmaceutically acceptable salts thereof.

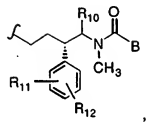
5. The method of Claim 1 wherein the compound is of Formula Ia:



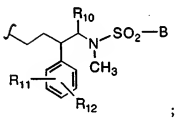
Ia

wherein:

R_1 is



, or



;

where B is selected from:

(a) phenyl, naphthyl, mono, di or tri-substituted phenyl, and mono, di or tri-substituted naphthyl wherein the substituents on phenyl or naphthyl are independently selected from: chloro, methyl, phenyl, C_{1-3}alkoxy, and CF_3;

(b) -CH_2phenyl, and mono or di-substituted -CH_2phenyl wherein the substituents on phenyl are independently selected from: chloro, methyl, phenyl, C_{1-3}alkoxy and CF_3;

(c) pyridyl, and mono di or tri-substituted pyridyl wherein the substituents on pyridyl are independently selected from: chloro, methyl, phenyl, C_{1-3}alkoxy and CF_3; and

(d) thiophene, and mono or disubstituted thiophene wherein the substituents on thiophene are independently selected from: chloro, methyl, phenyl, C_{1-3}alkoxy and CF_3;

Ar is mono substituted phenyl wherein the substituent is selected from the group consisting of:

(a) $-CH_2$-tetrazolyl,
(b) $-CH_2$-triazolyl,
(c) $-CH_2$-imidazolyl,
(d) $-CH_2-N(H)C(O)N(CH_3)_2$,
(e) $-CH_2-N(H)C(O)N(H)CH_3$,
(f) $-CH_2-N(H)C(O)CH_3$,
(g) $-CH_2-N(H)S(O)_2CH_3$,
(h) $-CH_2$-pyridyl,
(i) $-CH_2$-oxopyridyl,
(j) $-CH_2$-O-pyridyl, and
(k) mono or di-substituted purine wherein the substituents are selected from:
  (1') C_{1-3}alkyl,
  (2') C_{1-3}alkoxy,
  (3') fluoro,
  (4') hydrogen, and
  (5') fluoroC_{1-3}alkyl;

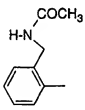
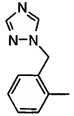
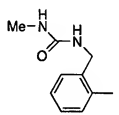
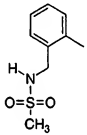
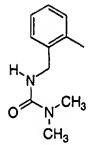
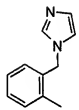
R_{10} is selected from: hydrogen, C_{1-3}alkyl, and phenyl;

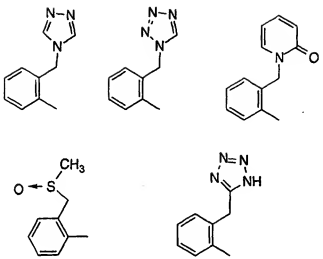
R_{11} and R_{12} are independently selected from: hydrogen, halogen, methyl, phenyl or CF_3;

and pharmaceutically acceptable salts thereof.

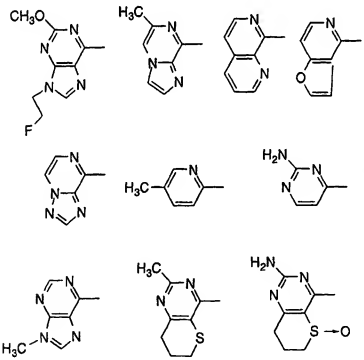
6. The method of Claim 5 wherein the compound of Formula Ia B is unsubstituted phenyl or unsubstituted thiophene.

7. The method of Claim 1 wherein the compound of Formula I Ar is selected from



8. The method of Claim 1 wherein the compound of Formula I Ar is selected from the group consisting of:



9. The method of Claim 1 wherein the compound is selected from the group consisting of:

(a) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-((2-acetylaminomethyl)-phenyl)-piperazine;

(b) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl-(methylamino))butyl)-4-(2-acetylaminomethylphenyl)-piperazine;

(c) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-((2-methylaminocarbonylamino-methyl) phenyl)-piperazine;

(d) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl (methylamino))butyl)-4-((2-dimethylaminocarbonylamino-methyl) phenyl)-piperazine;

(e) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-(2-methylsulfonylaminomethyl-phenyl)-piperazine;

(f) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl-(methylamino))butyl)-4-((2-methylaminocarbonylamino-methyl) phenyl)-piperazine;

(g) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl-(methylamino))butyl)-4-((2-dimethylaminocarbonylamino-methyl) phenyl)-piperazine;

(h) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl-(methylamino))butyl)-4-(2-methylsulfonylaminomethyl-phenyl)-piperazine;

(i) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-(2-((1'-imidazolyl)methyl)phenyl)-piperazine;

(j) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl-(methylamino))butyl)-4-(2-(1'-(1',2',4'-triazolyl)methyl-phenyl)-piperazine;

(k) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-(2-(1'-(1',2',4'-triazolyl)methyl-phenyl)-piperazine;

(l) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-(2-(1'-(1',2',3',4'-tetrazolyl)methylphenyl)-piperazine;

(m) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-(2-(3'-pyridyloxy)methylphenyl)-piperazine;

(n) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-(2-(1'-(2'(1'H)-pyridone)methyl-phenyl)-piperazine;

(o) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(2-amino-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine-5-oxide;

(p) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(2-methyl-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine-5-oxide;

(q) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(9-(2-fluoroethyl)-2-methoxy-purin-6-yl) piperazine;

(r) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(9-(2-methoxymethyl)-2-methoxy-purin-6-yl) piperazine;

(s) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(9-methyl-purin-6-yl)piperazine;

(t) 1-(3-((S)-(4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(9-methyl-purin-6-yl)piperazine;

(u) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(6-methyl-imidazo(1,2-a)pyrazin-1-yl) piperazine;

(v) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(1,7-naphthyridin-8-yl)piperazine;

(w) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(1,2,4-triazolo(1,5-a)pyrazin-8-yl)piperazine;

(x) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(5-methyl-pyrid-2-yl)piperazine;

(y) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-amino-pyrazin-4-yl)piperazine;

(z) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(furo(2,3-c)pyrid-4-yl))piperazine;

(aa) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-amino-7,8-dihydro-6H-thiopyrano-(3,2-d)pyrimid-4-yl)piperazine;

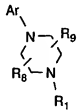
(ab) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-methyl-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine;

(ac) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-bis(trifluoromethyl)benzoyl)-(methylamino))butyl)-4-(1,2,4-triazolo(1,5-a)pyrazin-8-yl)piperazine; and

(ad) 1-(3-((S)-(4-Chlorophenyl))-4-(N-(3,5-bis(trifluoromethyl)benzoyl)-(methylamino))butyl)-4-(1,2,4-triazolo(1,5-a)pyrazin-8-yl)piperazine;

and pharmaceutically acceptable salts thereof.

10. A method for preventing infection by HIV, treating infection by HIV, delaying of the onset of AIDS, or treating AIDS comprising the administration to a patient of an effective amount of a compound of the formula:



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wherein the nitrogen attached to R_1 shown above is optionally quaternized with C_{1-4}alkyl or phenylC_{1-4}alkyl or is optionally present as the N-oxide (N^+O^-), and wherein:

R_1 is selected from a group consisting of:

linear or branched C_{1-8} alkyl, linear or branched C_{2-8} alkenyl, wherein the C_{1-8} alkyl or C_{2-8} alkenyl is optionally mono, di, tri or tetra substituted, the substituents independently selected from:

(a) hydroxy,
(b) oxo,
(c) cyano,
(d) halogen which is defined to include Br, Cl, I, and F,
(e) trifluoromethyl,
(f) phenyl or mono, di or tri-substituted phenyl, the substituents independently selected from
  (1') phenyl,
  (2') hydroxy,
  (3') C_{1-3}alkyl,
  (4') cyano,
  (5') halogen,
  (6') trifluoromethyl,

(7') -NR_6COR_7,
(8') -$NR_6CO_2R_7$,
(9') -NR_6CONHR_7,
(10') -$NR_6S(O)_jR_7$, wherein j is 1 or 2,
(11') -$CONR_6R_7$,
(12') -COR_6,
(13') -CO_2R_6,
(14') -OR_6,
(15') -$S(O)_kR_6$, wherein k is 0, 1 or 2,

(g) -NR_6R_7,
(h) -NR_6COR_7,
(i) -$NR_6CO_2R_7$,
(j) -NR_6CONHR_7,
(k) -$NR_6S(O)_j$-R_7,
(l) -$CONR_6R_7$,
(m) -COR_6,
(n) -CO_2R_6,
(o) -OR_6,
(p) -$S(O)_kR_6$,
(q) -NR_6CO-heteroaryl,
(r) -$NR_6S(O)_j$-heteroaryl, and
(s) heteroaryl, wherein heteroaryl is selected from the group consisting of:
(1') benzimidazolyl,
(2') benzofuranyl,
(3') benzoxazolyl,
(4') furanyl,
(5') imidazolyl,
(6') indolyl,
(7') isooxazolyl,
(8') isothiazolyl,
(9') oxadiazolyl,
(10') oxazolyl,
(11') pyrazinyl,

(12') pyrazolyl,
(13') pyridyl,
(14') pyrimidyl,
(15') pyrrolyl,
(16') quinolyl,
(17') tetrazolyl,
(18') thiadiazolyl,
(19') thiazolyl,
(20') thienyl, and
(21') triazolyl,

wherein the heteroaryl is unsubstituted or mono di or tri-substituted, the substituents independently selected from:

(a") phenyl,
(b") hydroxy,
(c") oxo,
(d") cyano,
(e") halogen, and
(f") trifluoromethyl;

Ar is selected from the group consisting of:

(1) phenyl,
(2) pyridyl,
(3) pyrimidyl,
(4) naphthyl,
(5) furyl,
(6) pyrryl,
(7) thienyl,
(8) isothiazolyl,
(9) imidazolyl,
(10) benzimidazolyl,
(11) tetrazolyl,
(12) pyrazinyl,
(13) quinolyl,
(14) isoquinolyl,

(15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,
(20) isoindolyl,
(21) purinyl,
(22) isoxazolyl,
(23) thiazolyl,
(24) oxazolyl,
(25) triazinyl, and
(26) benzthiazolyl,
(27) benzoxazolyl,
(28) imidazopyrazinyl,
(29) triazolopyrazinyl,
(30) naphthyridinyl,
(31) furopyridinyl,
(32) thiopyranopyrimidyl and the 5-oxide and 5-dioxide thereof,
(33) pyridazinyl,
(34) quinazolinyl,
(35) pteridinyl,
(36) triazolopyrimidyl,
(37) triazolopyrazinyl,
(38) thiapurinyl,
(39) oxapurinyl, and
(40) deazapurinyl,

wherein Ar items (1) to (40) are optionally mono or di-substituted, said substituents being independently selected from:

(a) C_{1-3} alkyl, unsubstituted or substituted with
(1') oxo,
(2') hydroxy,
(3') OR_6,
(4') halogen,
(5') trifluoromethyl,

(6') phenyl or mono, di or tri-substituted phenyl, the substituents independently selected from hydroxy, cyano, halogen, and trifluoromethyl,

(b) $-(CH_2)_nS(O)_k-(C_{1-6}$ alkyl), wherein n is 0, 1 or 2,

(c) $-(CH_2)_nS(O)j-NH_2$,

(d) $-(CH_2)_nS(O)j-NH(C_{1-6}$ alkyl),

(e) $-(CH_2)_nS(O)j-NHR_6$,

(f) $-(CH_2)_nS(O)j-NR_6-(C_{1-6}$ alkyl),

(g) $-(CH_2)_nCONH_2$,

(h) $-(CH_2)_nCONH-(C_{1-6}$ alkyl),

(i) $-(CH_2)_nCONHR_6$,

(j) $-(CH_2)_nCONR_6-(C_{1-6}$ alkyl),

(k) $-(CH_2)_nCO_2H$,

(l) $-(CH_2)_nCO_2-(C_{1-6}$ alkyl),

(m) $-(CH_2)_nNR_6R_7$,

(n) $-(CH_2)_nNH-C(O)-C_{1-6}$alkyl,

(o) $-(CH_2)_nNH-C(O)NH_2$,

(p) $-(CH_2)_nNH-C(O)NHC_{1-6}$alkyl,

(q) $-(CH_2)_nNH-C(O)N-(diC_{1-6}$ alkyl),

(r) $-(CH_2)_nNH-S(O)k-C_{1-6}$alkyl,

(s) $-(CH_2)_nN(C_{1-3}$alkyl)-C(O)-N(diC_{1-6} alkyl),

(t) $-(CH_2)_n$-heteroaryl, -C(O)-heteroaryl or $-(CH_2)_n$-O-heteroaryl , wherein the heteroaryl is selected from the group consisting of:

(1') benzimidazolyl,

(2') benzofuranyl,

(3') benzoxazolyl,

(4') furanyl,

(5') imidazolyl,

(6') indolyl,

(7') isooxazolyl,

(8') isothiazolyl,

(9') oxadiazolyl,

(10') oxazolyl,

(11') pyrazinyl,

(12') pyrazolyl,
(13') pyridyl or oxopyridyl,
(14') pyrimidyl,
(15') pyrrolyl,
(16') quinolyl,
(17') tetrazolyl,
(18') thiadiazolyl,
(19') thiazolyl,
(20') thienyl, and
(21') triazolyl,

wherein the heteroaryl group of items (1') to (21') is unsubstituted, mono, di or tri substituted, the substituents selected from:

(a') hydrogen,
(b') C_{1-6} alkyl, branched or unbranched, unsubstituted or mono or di-substituted, the substituents being selected from hydrogen and hydroxy,
(c') hydroxy,
(d') oxo,
(e') -OR_6,
(f') halogen,
(g') trifluoromethyl,
(h') nitro,
(i') cyano,
(j') -NHR_6,
(k') -NR_6R_7,
(l') -$NHCOR_6$,
(m') -NR_6COR_7,
(n') -$NHCO_2R_6$,
(o') -$NR_6CO_2R_7$,
(p') -$NHS(O)jR_6$,
(q') -$NR_6S(O)jR_7$,
(r') -$CONR_6R_7$,
(s') -COR_6,

(t') -CO_2R_6, and
(u') -S(O)$_j$$R_6$;

R_6 is selected from:

(1) hydrogen,
(2) C_{1-6} alkyl, or mono or di-substituted C_{1-6} alkyl, the substituents independently selected from:
  (a) phenyl,
  (b) hydroxy,
  (c) oxo,
  (d) cyano,
  (e) halogen,
  (f) trifluoromethyl, and
(3) phenyl or mono di or tri-substituted phenyl, the substituents independently selected from:
  (a) hydroxy,
  (b) C_{1-3}alkyl,
  (c) cyano,
  (d) halogen,
  (e) trifluoromethyl;

R_7 is selected from:

(1) hydrogen,
(2) C_{1-6} alkyl, or mono or di-substituted C_{1-6} alkyl, the substituents independently selected from:
  (a) phenyl unsubstituted or substituted with
    (1') hydroxy,
    (2') C_{1-3}alkyl,
    (3') cyano,
    (4') halogen,
    (5') trifluoromethyl,
    (6') C_{1-3}alkyloxy,
  (b) hydroxy,
  (c) oxo,

(d) cyano,
(e) halogen,
(f) trifluoromethyl,

(3) phenyl or mono di or tri-substituted phenyl, the substituents independently selected from:
(a) hydroxy,
(b) C_{1-3}alkyl,
(c) cyano,
(d) halogen,
(e) trifluoromethyl,

(4) naphthyl or mono di or tri-substituted naphthyl, the substituents independently selected from:
(a) hydroxy,
(b) C_{1-3}alkyl,
(c) cyano,
(d) halogen,
(e) trifluoromethyl,

(5) C_{1-3}alkyloxy;

or R_6 and R_7 are joined together to form a 5-, 6-, or 7-membered monocyclic saturated ring containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and in which the ring is unsubstituted or mono or di-substituted, the substituents independently selected from:
(1) hydroxy,
(2) oxo,
(3) cyano,
(4) halogen,
(5) trifluoromethyl,

R_8 and R_9 are each independently hydrogen or substituted C_{1-4}alkyl wherein the substitutent is selected from the group consisting of
(1) hydroxy,
(2) hydrogen,

(3) cyano,
(4) halogen,
(5) trifluoromethyl,
(6) C_{1-3}alkyloxy,

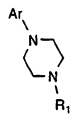
provided that when Ar is phenyl, pyridyl or pyrimidyl, then Ar is mono di or tri-substituted;

and further provided that when Ar is mono substituted phenyl, then the substituent is other than halo, hydroxy, -OC_{1-4}alkyl, CF_3 or C_{1-4}alkyl;

and further provided that when Ar is di- or tri-substituted, at least one of the substituents is other than halo, hydroxy, -OC_{1-4}alkyl, CF_3 or C_{1-4}alkyl;

and pharmaceutically acceptable salts thereof.

11. The method of Claim 10 wherein the compound is of Formula Ia:



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wherein:

R_1 is selected from a group consisting of:

C_3, C_4, C_5, C_6, C_7, C_8 linear or branched alkyl, unsubstituted or mono, di or tri-substituted, the substituents independently selected from:

(a) hydroxy,
(b) Cl or F,
(c) phenyl or mono, di or tri-substituted phenyl, the substituents independently selected from:
(1') phenyl,

(2') hydroxy,
(3') C_{1-3}alkyl,
(4') cyano,
(5') halogen,
(6') trifluoromethyl,

(d) -NR_6CO-R_7, wherein R_6 is hydrogen or C_{1-3} alkyl and R_7 is phenyl optionally substituted with Cl, F, CF_3 or C_{1-3}alkyl,

(e) -COR_6,

(f) -OR_6,

(g) -$NR_6S(O)j$-R_7, where j is 1 or 2,

(h) -$NR_6S(O)j$-heteroaryl, wherein heteroaryl is selected from the group consisting of:
(1') benzimidazolyl,
(2') benzofuranyl,
(3') benzoxazolyl,
(4') furanyl,
(5') imidazolyl,
(6') indolyl,
(7') isooxazolyl,
(8') isothiazolyl,
(9') oxadiazolyl,
(10') oxazolyl,
(11') pyrazinyl,
(12') pyrazolyl,
(13') pyridyl,
(14') pyrimidyl,
(15') pyrrolyl,
(16') quinolyl,
(17') tetrazolyl,
(18') thiadiazolyl,
(19') thiazolyl,
(20') thienyl, and
(21') triazolyl,

wherein the heteroaryl is unsubstituted or mono di or

tri-substituted, the substituents independently selected from:

(a') phenyl,
(b') hydroxy,
(c') oxo,
(d') cyano,
(e') halogen, and
(f') trifluoromethyl;

Ar is selected from the group consisting of:

(1) phenyl,
(2) pyrazinyl,
(3) pyrazolyl,
(4) pyridyl,
(5) pyrimidyl, and
(6) thienyl,

wherein the Ar is unsubstituted or mono or di-substituted, and substituents are independently selected from:

(a) C_{1-3} alkyl, unsubstituted or substituted with
  (1') oxo,
  (2') hydroxy,
  (3') OR_6,
  (4') halogen, and
  (5') trifluoromethyl,
(b) $CONR_6$-(C_{1-2} alkyl),
(c) CO_2H,
(d) CO_2-(C_{1-2} alkyl),
(e) CH_2NR_6-(C_{1-2} alkyl),
(f) CH_2NH-C(O)-C_{1-3}alkyl,
(h) CH_2NH-C(O)NH_2,
(i) CH_2NH-C(O)NHC_{1-3}alkyl,
(j) CH_2NH-C(O)N-diC_{1-3} alkyl),
(k) CH_2NH-S(O)j-C_{1-3}alkyl,
(l) CH_2-heteroaryl, with the heteroaryl is selected from the group consisting of:

(1') imidazolyl,
(2') oxazolyl,
(3') pyridyl,
(4') tetrazolyl,
(5') triazolyl,
and the heteroaryl is unsubstituted, mono, di or tri-substituted, where the substituents selected from:
(a') hydrogen,
(b') C_{1-6} alkyl, branched or unbranched, unsubstituted or mono or di-substituted, the substituents being selected from hydrogen and hydroxy;

and pharmaceutically acceptable salts thereof.

12. The method of Claim 10 wherein the compound R_1 is selected from a group consisting of:
C_4, C_5, C_6, C_7 or C_8 linear or branched alkyl, which is mono, di- or tri-substituted, where the substituents are independently selected from:
(a) hydroxy,
(b) Cl or F,
(c) phenyl or mono or di-substituted phenyl, where the substituents are independently selected from:
(1') hydroxy,
(2') methyl or ethyl,
(3') Cl or F,
(4') trifluoromethyl,
(d) $-NR_6COR_7$, wherein R_6 is methyl and R_7 is phenyl optionally substituted with halo, CF_3, C_{1-3}alkyl or C_{1-3}alkoxy, and
(e) $-NR_6S(O)j-R_7$, where j is 1 or 2;

and pharmaceutically acceptable salts thereof.

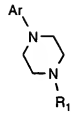
13. The method of Claim 10 wherein the compound Ar is mono substituted or di-substituted phenyl,

wherein the substituents are selected from the group consisting of:

(a) C_{1-3} alkyl, unsubstituted or substituted with
  (1') oxo,
  (2') hydroxy, or
  (3') OR_6, wherein R_6 is hydrogen or C_{1-3} alkyl,
(b) $-CH_2NR_6-(C_{1-2}$ alkyl),
(c) $-CH_2NH-C(O)-C_{1-3}$alkyl,
(d) $-CH_2NH-C(O)NH_2$,
(i) $-CH_2NH-C(O)NHC_{1-3}$alkyl,
(j) $-CH_2NH-C(O)N-diC_{1-3}$ alkyl),
(k) $-CH_2NH-S(O)j-C_{1-3}$alkyl,
(l) $-CH_2$-heteroaryl, where heteroaryl is selected from the group consisting of:
  (1') imidazolyl,
  (2') oxazolyl,
  (3') pyridyl,
  (4') tetrazolyl,
  (5') triazolyl,
  and where heteroaryl is unsubstituted, mono, di or tri substituted, where the substituents are independently selected from:
    (a') hydrogen,
    (b') C_{1-6} alkyl, branched or unbranched, unsubstituted or mono or disubstituted, where the substituents are selected from: hydrogen and hydroxy;

and pharmaceutically acceptable salts thereof.

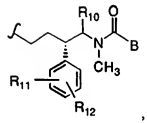
14. The method of Claim 10 wherein the compound is of Formula Ia:



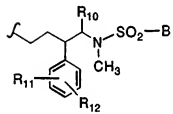
Ia

wherein:

R_1 is



, or



;

where B is selected from:

(a) phenyl, naphthyl, mono, di or tri-substituted phenyl, and mono, di or tri-substituted naphthyl wherein the substituents on phenyl or naphthyl are independently selected from: chloro, methyl, phenyl, C_{1-3}alkoxy, and CF_3;

(b) -CH_2phenyl, and mono or di-substituted -CH_2phenyl wherein the substituents on phenyl are independently selected from: chloro, methyl, phenyl, C_{1-3}alkoxy and CF_3;

(c) pyridyl, and mono di or tri-substituted pyridyl wherein the substituents on pyridyl are independently selected from: chloro, methyl, phenyl, C_{1-3}alkoxy and CF_3; and

(d) thiophene, and mono or disubstituted thiophene wherein the substituents on thiophene are independently selected from: chloro, methyl, phenyl, C_{1-3}alkoxy and CF_3;

Ar is mono substituted phenyl wherein the substituent is selected from the group consisting of:

(a) $-CH_2$-tetrazolyl,
(b) $-CH_2$-triazolyl,
(c) $-CH_2$-imidazolyl,
(d) $-CH_2-N(H)C(O)N(CH_3)_2$,
(e) $-CH_2-N(H)C(O)N(H)CH_3$,
(f) $-CH_2-N(H)C(O)CH_3$,
(g) $-CH_2-N(H)S(O)_2CH_3$,
(h) $-CH_2$-pyridyl,
(i) $-CH_2$-oxopyridyl,
(j) $-CH_2$-O-pyridyl, and
(k) mono or di-substituted purine wherein the substituents are selected from:
(1') C_{1-3}alkyl,
(2') C_{1-3}alkoxy,
(3') fluoro,
(4') hydrogen, and
(5') fluoroC_{1-3}alkyl;

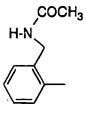
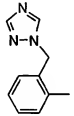
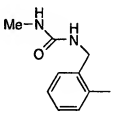
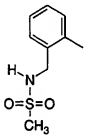
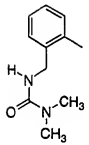
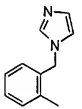
R_{10} is selected from: hydrogen, C_{1-3}alkyl, and phenyl;

R_{11} and R_{12} are independently selected from: hydrogen, halogen, methyl, phenyl or CF_3;

and pharmaceutically acceptable salts thereof.

15. The method of Claim 4 wherein the compound of Formula Ia B is unsubstituted phenyl or unsubstituted thiophene.

16. The method of Claim 10 wherein the compound of Formula I Ar is selected from

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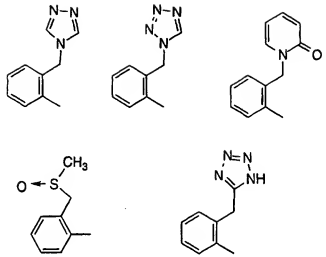
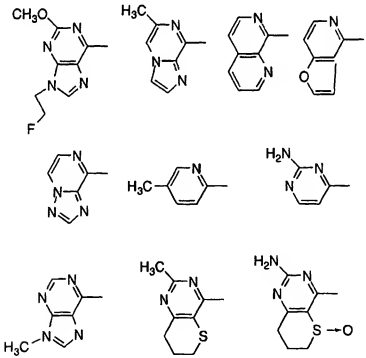


17. The method of Claim 10 wherein the compound of Formula I Ar is selected from the group consisting of:



18. The method of Claim 10 wherein the compound is selected from the group consisting of:

(a) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-((2-acetylaminomethyl)-phenyl)-piperazine;

(b) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl-(methylamino))butyl)-4-(2-acetylaminomethylphenyl)-piperazine;

(c) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-((2-methylaminocarbonylamino-methyl) phenyl)-piperazine;

(d) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl (methylamino))butyl)-4-((2-dimethylaminocarbonylamino-methyl) phenyl)-piperazine;

(e) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-(2-methylsulfonylaminomethyl-phenyl)-piperazine;

(f) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl-(methylamino))butyl)-4-((2-methylaminocarbonylamino-methyl) phenyl)-piperazine;

(g) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl-(methylamino))butyl)-4-((2-dimethylaminocarbonylamino-methyl) phenyl)-piperazine;

(h) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl-(methylamino))butyl)-4-(2-methylsulfonylaminomethyl-phenyl)-piperazine;

(i) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-(2-((1'-imidazolyl)methyl)phenyl)-piperazine;

(j) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl-(methylamino))butyl)-4-(2-(1'-(1',2',4'-triazolyl)methyl-phenyl)-piperazine;

(k) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-(2-(1'-(1',2',4'-triazolyl)methyl-phenyl)-piperazine;

(l) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-(2-(1'-(1',2',3',4'-tetrazolyl)methylphenyl)-piperazine;

(m) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-(2-(3'-pyridyloxy)methylphenyl)-piperazine;

(n) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl-(methylamino))butyl)-4-(2-(1'-(2'(1'H)-pyridone)methyl-phenyl)-piperazine;

(o) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(2-amino-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine-5-oxide;

(p) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-(2-methyl-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine-5-oxide;

(q) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(9-(2-fluoroethyl)-2-methoxy-purin-6-yl) piperazine;

(r) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(9-(2-methoxymethyl)-2-methoxy-purin-6-yl) piperazine;

(s) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(9-methyl-purin-6-yl)piperazine;

(t) 1-(3-((S)-(4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(9-methyl-purin-6-yl)piperazine;

(u) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(6-methyl-imidazo(1,2-a)pyrazin-1-yl) piperazine;

(v) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(1,7-naphthyridin-8-yl)piperazine;

(w) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(1,2,4-triazolo(1,5-a)pyrazin-8-yl)piperazine;

(x) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(5-methyl-pyrid-2-yl)piperazine;

(y) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-amino-pyrazin-4-yl)piperazine;

(z) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(furo(2,3-c)pyrid-4-yl))piperazine;

(aa) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-amino-7,8-dihydro-6H-thiopyrano-(3,2-d)pyrimid-4-yl)piperazine;

(ab) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-dimethylbenzoyl)-(methylamino))butyl)-4-(2-methyl-7,8-dihydro-6H-thiopyrano(3,2-d)pyrimid-4-yl)piperazine;

(ac) 1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-(3,5-bis(trifluoromethyl)benzoyl)-(methylamino))butyl)-4-(1,2,4-triazolo(1,5-a)pyrazin-8-yl)piperazine; and

(ad) 1-(3-((S)-(4-Chlorophenyl))-4-(N-(3,5-bis(trifluoromethyl)benzoyl)-(methylamino))butyl)-4-(1,2,4-triazolo(1,5-a)pyrazin-8-yl)piperazine;
and pharmaceutically acceptable salts thereof.

19. A compound which is selected from the group consisting of:

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((R)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-((2-nitro)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-((2-amino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methylamino))butyl)-4-((2-formylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-n-butyrylamino)phenyl)-piperazine;
1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-n-propionylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-(3-methylbut-2-enoylamino)phenyl)-piperazine;
1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-methoxycarbonylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-ethoxycarbonylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-methansulfonylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-4-methoxybenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,4-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-benzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-4-chlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-chlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-2-chlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-4-methylbenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-4-ethylbenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-trifluoromethylbenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-4-i-propyloxybenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-methyl-4-chlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethoxybenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-2,6-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-trifluoromethyl-4-fluorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-2,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-2,3-dichlorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-2-trifluoromethylbenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-naphth-1-oyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-naphth-2-oyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-4-trifluoromethylbenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-2-methoxybenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-fluorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-bis-trifluoromethylbenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-cyanobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-nitrobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethyl-4-fluorobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3-iodobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dibromobenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dimethylbenzoyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-acetyl)-(methyl-amino))butyl)-4-((2-acetylamino)phenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-(4-trifluoromethylphenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-(4-acetylphenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-(4-methylphenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-(4-chlorophenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-(4-fluorophenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-(4-nitrophenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-(3-trifluoromethylphenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-(3-methylphenyl)-piperazine;

1-(3-((S)-(3,4-Dichlorophenyl))-4-(N-3,5-dichlorobenzoyl)-(methyl-amino))butyl)-4-(2-cyanophenyl)-piperazine;

1-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-phenylpiperazine;

1-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-(2-methylphenyl)piperazine;

1-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-(3-hydroxyquinoxalin-2-yl)piperazine;

1-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-(4-pyridyl)piperazine;

1-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-benzylpiperazine;

1-(3-((S)-(3-Chlorophenyl))-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-(2-methoxyphenyl)piperazine;

1-(3-((R,S)-Phenyl)-4-(N-(phenylsulfonyl)(methylamino))butyl)-4-(pyrimidin-2-yl)piperazine;

and pharmaceutically acceptable salts thereof.